Survey of Genome Science Corporations

Contract Report
prepared for the Office of Technology Assessment
US Congress

March 1994

This report is based on telephone, electronic, and letter solicitations of corporate firms and private research groups engaged in genome research as part of a long-term commercialization strategy. I contacted the firms and research centers by letter, phone, fax, or electronic mail and asked for any publicly available information to be sent to me. I indicated that I would be preparing a précis of the information for OTA, as background and perhaps to result in text boxes for the forthcoming report on DNA patenting. I also indicated that another purpose of the contact was to provide commercial firms — especially those likely to be affected directly by DNA patent policies — an opportunity to give OTA input, including suggestions for policy options, comments on possible policy options already under discussion, observations about the NIH patent application, and perspectives on other recent historical events. An initial draft was sent the first week of January for comment, and most firms responded by the end of February. I incorporated their comments and new documents into the March 1994 revision. Finally, the initial public offerings by Incyte Pharmaceuticals, Inc., and Human Genome Sciences, Inc., were accompanied by documents filed with the Securities and Exchange Commission. Those documents were reviewed, and those germane to the discussion here are noted in the bibliography.

This March 1994 draft differs from the January draft chiefly in incorporating corrections from the various firms, addition of text as requested by them, and the opportunity to review the SEC-filed documents for Incyte and Human Genome Sciences. In addition, Collaborative Research compiled a comprehensive list of its federal research grants and contracts that is appended. Several companies have contributed statements on patent law that are directly relevant, and may provide useful quotes for the OTA report.

The following section goes through each firm serially. The firms contacted were:

Collaborative Research, Inc.
Darwin Molecular Corp.
Human Genome Sciences, Inc.
Incyte Pharmaceuticals, Inc.
Mercator Genetics, Inc.
Millennium Pharmaceuticals, Inc.,
Myriad Genetics, Inc., and
Sequana Therapeutics, Inc.

In addition, I contacted two privately funded research centers known to be pursuing cDNA patents:

The Institute for Genomic Research, and
Sagami Chemical Research Center, which also includes some information about other private sector and prefectural (local government) activities in Japan.

I append a list of references that were cited, and a bibliography that includes items pulled from my files or sent by the companies or SEC. Citation information is missing for some references, generally those I got directly from the companies. While most news articles are pretty good in sketching the outlines and strategic thrust of the firms, many contain inaccuracies about dates, the order of events, dollar amounts, management relationships, and the linkage between science and corporate strategy. Press accounts should not be relied upon for accurate numbers or scientific background. The articles in *Business Week, Nature* and *Science* are more reliable than the trade sheets, which seem most prone to inaccuracy and superficiality. The press releases directly from companies are presumably accurate about dollars and events, although several have a fair amount of topspin when it comes to interpretation. Treat them like you would a serve from Pete Sampras, with respect but also caution.

Collaborative Research, Inc.

Address: 100 Beaver Street
Waltham, MA 02154
(R&D facility 1365 Main Street)

Phone: 617-487-7979
fax 617-487-7960

Founded: 1961

President and CEO: Robert J. Hennessey

Vice President, Business Development: John P. Richard

Senior Vice President, Research and Development: Gerald F. Vovis

Board of Directors: Orrie Friedman (chair), Mark D. Friedman (Mistui & Co.), (Hennessey), Lawrence Levy (Northern Ventures Corp.), Donald J. McCarren (ImmunoGen, Inc.), Stephen Rauscher (Pharmedic Co.), Seymour Rothchild, and Paul C. Zamecnik (Worcester Foundation for Experimental Biology)

Scientific Advisory Board: none, company is thinking of reconstituting a scientific advisory board, but has made no final decision.

Capitalization: Collaborative Research, Inc., has its stock publicly traded on NASDAQ (as CRIC). Its 1993 high was 4 3/4 and its low 1 1/8[3]. It closed the year at 4, rebounding after it sold off its diagnostics operation.

Its financial status is much more complex than the other companies surveyed because it has existed for more than a decade, has a revenue stream from products and services, and is carrying out grant and contract research for NIH and Abbott Laboratories. CRI's total assets peaked in 1989, at $15 million, and stood at $5.3 million at the end of 1993. Stockholder equity was $13 million in 1989 and $3.5 million at the end of fiscal year 1993. Total working capital peaked in

1991 at $8.8 million, and now stands at $3.3 million. The main reason to sell off the diagnostics service was to lower the burn rate, and the net loss decreased from $772,000 in first quarter 1993 to $203,000 in 1994[16].

CRI notes that "with the current cash balance and reduced cash burn rate, we will be able to support operations for the foreseeable future. However, substantial additional investment is necessary before new products can be developed and profitability can be achieved" (p. 2)[10]. The strategy to attract new capital is to develop strategic alliances with major pharmaceutical and other health care companies, and CRI is "exploring opportunities to raise additional funds through various financing vehicles" (p. 3)[10].

Research Plan: Collaborative Research, Inc., was established in 1961 to pursue contract research on cancer drugs for NCI. It was founded by a Brandeis professor, Orrie Friedman. An initial $250,000 per year, five-year contract was its first effort. The Mansfield amendment, intended to thwart defense contract abuses, led to loss of several contracts in the late 1960s, and the staff dwindled from 40 to 24. CRI was thus founded on federal contract research, and its genome research strategy continues this philosophy. It now has 16 federal grants and contracts[80].

Collaborative Research, Inc., has long been engaged in the full range of genomic research techniques. A CRI marker was the first to link to the cystic fibrosis gene. The linkage was discovered under a collaboration between CRI and Lap-Chee Tsui at the University of Toronto in 1985[73]. CRI's group participated in the CEPH consortium, contributing the second largest number of markers of any group in it (the largest contributor was the University of Utah/Howard Hughes Medical Institute). CRI invested $11 million of its own funds into RFLP mapping and related projects, starting a decade ago (p. 2)[10]. Helen Donis-Keller, as head of the CRI team, was lead author of the first genetic linkage map of the human genome in 1987[15].

CRI's annual report to stockholders (in contrast to the SEC form 10-K annual report, which is the source of most other quotes here), accurately notes that CRI "helped to stimulate the beginning of the Human Genome Project " (p. 2)[10]. CRI and the University of Utah's efforts at genetic linkage map construction highlighted the failure of the federal government to build up the long-term infrastructure for large-scale genetics in the period 1985-1988, when the genome project was being debated vigorously in Congress. While this was controversial at the time, the RFLP map construction project established CRI as a significant scientific force.

The RFLP technique naturally led to a genetic diagnostics capacity, and the company began to do genetic testing commercially as a service. CRI operated this service for several years, but it consistently lost money, despite rapid percentage revenue increases from 1989-1993. On June 27, 1993, the diagnostic testing operation was sold to Dianon, a cancer and genetic testing business, for $900,000, with another possible $300,000 contingent on unspecified conditions (p. 39)[12]. The 1993 third quarter report from President Robert J. Hennessey states that the sale "has given us the time and opportunity to implement the Company's core strategy of licensing, discovering, and developing genetically-based proprietary therapeutics and pharmaceuticals"[22].

CRI states that its strategy is "now well defined and clearly focused: We are applying advances from human genome research to the development of proprietary drugs for the treatment of infectious diseases and other major diseases. Specific projects that are receiving priority attention are tuberculosis, manic depression, asthma, and a variety of cancers"[22]. The strategy is to find genetic linkage, locate a gene and isolate it (or them) — the positional cloning approach [13; 14], but also adding a dimension of sequencing, as noted below. CRI has an especially rich set of markers for chromosome 7 (a legacy of the CF hunt) and also has a 92% complete physical map of chromosome 10 (p. 6)[12], and extensive markers for chromosome 20.

More recently, CRI has turned to high throughput sequencing as another means of identifying useful genes. It is also building up sequencing capacity, and has submitted a grant to perform genomic sequencing of those chromosomes it has been mapping intensively

(chromosomes 10 and 20). This would place it intermediate between the positional cloning companies and those doing cDNA sequencing. CRI is not doing cDNA sequencing of human DNA, although it continues to prepare DNA templates for NINDS to do so under a contract. It licensed George Church's semi-automated multiplex sequencing method from Harvard Medical School, and has contracts with NINDS, NCHGR, and NIGMS. The NINDS contract is for $1.5 million over 3 years to continue to prepare DNA templates, a legacy of Craig Venter's cDNA sequencing efforts[79]. (CRI prepared the DNA for that now-famous effort.) CRI also received a phase II SBIR grant from NCHGR, in the amount of $500,000 over two years, to develop the multiplex sequencing technique[79]. The idea is now to apply that technique to continue from physical mapping of chromosomal DNA done under a phase II SBIR grant that refined the linkage and physical maps for chromosomes 10 and 20[19].

In addition, CRI has a 3-year, $5 million contract with NCHGR to sequence the genomes of *Mycobacterium tuberculosis* and *M. leprae*, the organisms that cause tuberculosis and leprosy, respectively[63; 80]. This follows from a philosophy that the genome project has focused on the human genome, but "the fastest therapeutic advances from genomics will come instead from analyzing non-human genomes--specifically the genomes of pathogenic organisms" [11]. As of 29 November 1993, this effort had yielded 700,000 base pairs of sequence, and 600 full-length mycobacterial genes[63]. In a 31 December statement, CRI notes that this effort, supported by WHO and NIH, produced 10 million bases of raw sequence, and accounted for a quarter of the *M. leprae* genome [11]. This line of research has led to patent applications for over 600 mycobacterial genes [11], although the scope of relevant claims are not specified (p. 12)[12]. CRI has a $100,000 one-year contract with the National Institute of Environmental Health Science to search for mutations. This contract has four one-year options. It also has another phase II SBIR grant, from the National Institute of General Medical Sciences, for $500,000 over two years beginning 1 January 1993. This SBIR is intended to develop a testing procedure to identify multiple mutant alleles, for application to disorders such as CF, based on multiplexing (although

it is not clear whether from multiplex sequencing or some other form of multiplex probe or allele analysis)[18].

In 1990, CRI signed an agreement with the Health Sciences Research Institute of Yokohama that gave HSRI exclusive Japanese distribution rights for CRI's probes. In 1993, CRI signed an agreement with Immuno-Cor, to use its structural algorithms to screen cDNA libraries, and CRI also purchased an equity share in Immuno-Cor (the amount is not specified, and the only line item that might cover this is "payments for net assets acquired," of $268,500, which presumably indicates the maximum CRI could have paid for Immuno-Cor equity) (pp. 10, 37)[12]. CRI also signed an agreement in 1993 with Abbott Laboratories, but the purpose, amount of funding, and intellectual property agreements are not stated.

Comments on DNA patenting and technology transfer: CRI issued a public statement lauding NIH Director Harold Varmus's decision to abandon the EST patent applications filed by NIH in 1991 and 1992[51]. This statement is also a policy statement on their own patent strategy. "It has always been our policy to seek patent protection for gene sequences that meet the requirements of US Patent Law... We have not submitted patent applications for gene fragments because we believe that in most cases fragments have no defined utility and therefore should be unpatentable. Rather than use partial sequences, Collaborative Research has based its patent claims on complete genes. For example, this is the strategy we have taken in our recent patent applications for a broad family of tuberculosis and mycobacterial genes" [51].

CRI held an exclusive license to a patent application on the original RFLP technique (based on the Botstein, White, Skolnick, and Davis paper of 1980[7]). If this patent had issued, rather than being abandoned after many years' review in the Patent and Trademark Office, CRI would have had a distinctive edge for the first wave of diagnostic tests based on RFLPs. This exclusive license might have made life more difficult for companies and services, such as Integrated Genetics and university-associated testing services, that did not have the RFLP license.

The claims in the original patent application for the CF linkage were quite broad, claiming the ultimate gene and any markers discovered closer to it. That patent was abandoned when it became clear the cost of pursuing and defending it would not be balanced by financial benefits, especially after the CF gene itself was found, and a patent filed on behalf of the University of Michigan and its collaborators [23].

CRI retains exclusive worldwide rights to computer-assisted multiplex sequencing, a technique developed by George Church at Harvard Medical School, which holds the patent[63].

CRI does not state the number nor scope of its current patents. The Company has received patents for a number of processes or products in both the United States and foreign countries relating to rennin, EMIA, prourokinase (PUK) modification, PUK potentiation by streptokinase, secretion and production of heterologous proteins in yeast and anti-calculus agent" (pp. 10-11)[12]. CRI has applied for patents from its mycobacterial sequencing efforts (p. 12), covering "a broad family of tuberculosis and mycobacterial genes," but does not stipulate a scope of claims or define whether the applications cover process or composition of matter. The annual report goes on to state that "the Company has other patent applications pending in both the United States and abroad" (p. 12)[12].

CRI receives royalty income from Dow Chemical. CRI's royalties flow from contract research undertaken for Dow under an agreement that ended in 1985 (with the patent issued in 1988) to clone and produce rennin, an enzyme used in cheese production and other dairy processing, with CRI "granted the Company patent claims covering aspects of the production of recombinant rennin in cells, including yeast and bacteria" (p. 11)[12].

Rennin went on the market following FDA approval in 1990, but CRI received no royalties until 1992. The agreement with Dow stipulated that Dow would pay royalties to CRI only after Dow's own investments were repaid. CRI's income from royalty payments was $123,045 in 1993 and $74,683 in 1992. A US interference action concerning the rennin patent was settled.

In the UK, the patent is being challenged as invalid, with action pending. The 1993 annual report is deliberately vague about who the other parties are in both disputes, or the nature of the US settlement, saying only that it "expects to receive another US patent for rennin based on the application in the interference" (p. 11)[12].

While many instrumentation companies have accepted NIH and DOE grants to develop inventions, CRI stands alone among the companies surveyed in having received two large sequencing contracts ($6.5 million in aggregate over 3 years, NINDS and NCHGR), two SBIR phase II grants ($500,000/2 years each, from NCHGR and NIGMS for multiplex sequencing and multiple-allele genetic testing, respectively), and a $100,000 1-year (renewable) contract with NIEHS. It also has grants or contracts with the National Cancer Institute (for probes) with the Department of Veterans' Affairs (to make lymphoblast cell lines as part of a project on the genetics of schizophrenia), the Muscular Dystrophy Association (to clone the facioscapulohumeral dystrophy gene on 4q), the Department of Energy (to make a 5X YAC library), the National Institute of Mental Health (to locate the gene for bipolar disorder, and an SBIR contract for make a standard marker panel for linkage). In total, CRI has 16 grants and contracts (15 federal plus the Muscular Dystrophy Association), of differing sizes, amounts, and duration (see appendix submitted by CRI). In aggregate, the contracts and grants cover a significant fraction of CRI's operating expenses.

CRI's receipt of government grants and contracts clearly indicates a faith in technology transfer law quite different from some other companies, including all the other DNA sequencing and positional cloning companies surveyed. By way of contrast, Human Genome Sciences, Inc., bought out TIGR's DOE grant application to avoid "contamination" by government patent rights [33; 34]. CRI is explicitly pursuing government grants and contracts for genome research as a central feature of its genome research commercialization strategy. In this regard, it is much more similar to the first generation of biotechnology companies that derived protein pharmaceuticals from research that was often university-based than it is to the other startup genome research

companies surveyed. Indeed, given its origin as a federal contract research firm, it is adhering in genome research to its long tradition, although it now hopes to use those federal contracts to launch into diagnostic and therapeutic products[23].

At the interview with CRI corporate officers, we devoted a half hour or so to discussing any messages they believed it would be useful to transmit to Congress. I summarize a long discussion into a few points. First, any reach-through clauses, along the lines of the HHS "reasonable pricing" clause under CRADAs, would be devastating to CRI's commercial opportunities. The company is not immediately concerned with this, as they have no such clauses with their current SBIR grants and federal contracts, and they are governed not by the Federal Technology Transfer Act, but by Bayh-Dole and amendments. They are pursuing no CRADA agreements at present and do not foresee them in the near future. They also expressed concern about the possibility that some time in the future the domestic manufacturing preference embodied in Bayh-Dole might "scare off" a foreign pharmaceutical firm from a prospective deal, but it has not been an issue to date. They also expressed doubts that the domestic manufacture clause was the most effective way to capture jobs and income from US federal research investments, because in pharmaceuticals, manufacture is a very small fraction of the value-added.

CRI officers observed that in sequencing, patent protection is likely to be less important than subtle improvements in the way of trade secrets and labcraft.

They raised a point about intramural NIH research possibly emerging as a direct, highly subsidized, competitor for some of their work, particularly the gene-hunting enterprise at NCHGR. One particular spin on this is that government laboratories enjoy a royalty-free license for any inventions discovered under federal grants or contracts. It might be possible, therefore, for NIH laboratories to use CRI inventions without payment, while CRI (and other private firms) would have to pay licenses for inventions derived from government-sponsored research, whether done intramurally or by a grantee or contractor who holds the patent rights.

Finally, Robert Hennessey observed that the US is quite open to foreign collaboration with its research grants and through its universities. He has worked abroad with several pharmaceutical firms, and has been impressed that foreign universities and research ministries are far less open to collaboration with US corporations, and he believes this may emerge as a more important issue in the future.

Darwin Molecular Corporation

Address: 22025 20th Avenue, SE
Suite 1000
Bothell, Washington 98021

Phone: 206-489-8000
206-489-8020 fax
mark@darwin.com CEO Internet address

Founded: 1993

President and CEO: Mark L. Pearson

Vice-President, Research and Development: David J. Galas

Founders (both business and scientific directors): Ronald E. Cape, Chairman of the Board; Lloyd E. Cotsen, Director; Leroy E. Hood, Scientific Advisor; Gerald F. Joyce, Scientific Advisor; Lawrence A. Loeb, Chairman, Scientific Advisory Board; George B. Rathmann, Investor; Julius Rebek, Scientific Advisor

Capitalization: Not stated, other than to note investments of unspecified size by Rathmann and information contact with StratiPoint Group, Inc. of San Francisco. Several articles noted aspirations of $50 million in start-up funding, but these are nonspecific.

Research plan: Darwin proposes to combine rapid DNA sequencing, informatics and directed molecular evolution to screen and amplify, and mutate potential pharmaceutical compounds rapidly. The company promises to bring together strong DNA sequencing capacity with a high-power informatics team and to identify promising compounds by means of molecular evolution techniques. Molecular evolution is basically a general description (like "desk-top publishing") of a process that entails selecting for desired characteristics (e.g., strong binding to a known ligand), amplifying the selected molecule (be it nucleic acid or a protein covalently linked to its corresponding gene, or unique part of that gene), and mutating the amplified molecules to generate another population of molecules to go through the selection-amplification-mutation

cycle[6; 17; 35; 44; 60]. Evolutionary considerations (limits on duration and the degree of structural variety available at any given time in any given organism) have limited nature's ability to experiment with the full range of possible shapes and sizes of molecules, and so new combinations of amino acid sequences (and the nucleic acids coding for them) may well produce new and useful functions[24]. The theory is that directed evolution will open the path to small molecules that avoid the problems of large protein pharmaceuticals, and also should enable precise focus on small functional domains that may be therapeutically useful. The point is that there is likely room for improvement over nature, and now investigators are refining techniques for filling this space rapidly.

The company's literature indicates a research focus on drugs to treat cancer, AIDS, and immune dysfunction. The public information packet also cites heart disease once as a potential target for molecular evolution-driven drug discovery. The intention is to identify small molecules whose composition and use can be protected by patent and marketed as pharmaceuticals. The native DNA sequence of a gene would, at Darwin, presumably be merely the starting point for a multi-cycle process that would focus on smaller molecules with progressively refined characteristics (tighter binding, greater stability, broader temperature range, etc.).

Darwin's scientific and business investors are a blue-chip crowd. Mark Pearson was with NCI, then DuPont, and DuPont-Merck before joining Darwin as its President and CEO. David Galas, the Vice President for R&D, was head of the Office of Health and Environmental Research at the Department of Energy, home of the DOE's Human Genome Initiative. Before that, he was well known as a molecular biologist from the University of Southern California. Leroy Hood is, of course, extremely well known in genome and biotechnology instrumentation circles. Lawrence Loeb, Gerald Joyce, and Julius Rebek are all luminaries in the molecular evolution field. The affiliated scientists bring background in DNA structural analysis, molecular evolution, neuroscience, RNA chemistry, protein chemistry, organic chemistry and other fields.

George Rathmann, an investor in the company, was president of Amgen during its highly successful startup phase, then left to found Icos. Ronald Cape founded Cetus Corporation in 1972, serving as CEO and President until 1986 and again briefly in 1990-1991, before Cetus merged with Chiron and sold PCR rights to Hoffmann-La Roche. Lloyd Cotsen, another investor, is President and Chairman of the Board of Neutrogena Corp. He has been President of Neutrogena since 1973, and Chairman since 1991.

The business strategy is to initially form alliances with larger pharmaceutical houses and biotech companies, using Darwin as the drug discovery front-end to a therapeutic agent discovery and selection process, licensing out for clinical testing and marketing. Like all the other genome startup companies surveyed, Darwin's rhetoric indicates its aspirations a hope eventually to become a vertically integrated pharmaceutical firm.

Darwin is negotiating to acquire process patent rights for some molecular evolution techniques, and has filed patent applications in other unspecified areas.

Darwin's distinctive features are a highly distinguished group of scientific advisors, a well known group of investors from other biotechnology companies, and a novel approach, using molecular evolution techniques, to produce small organic molecules. Several companies are pursuing genome-scale research as a drug discovery front end, and others are pursuing molecular evolution to one degree or another, but Darwin appears unique in combining the approaches, or at least doing so explicitly and prominently in its business plan.

Comments on DNA patenting and technology transfer: David Galas's position at DOE was that patent claims should be pursued vigorously, but the scope of utility claims should be relatively narrow and tied to known function and use. He was a notable critic of the NIH patent application. In response to the January draft, and to a specific request, Diane Isonaka of Darwin submitted the following statement on intellectual property protections, on behalf of herself, David Galas, and Mark Pearson at Darwin Molecular Corp.:

The management at Darwin Molecular has been involved in the discussions relative to DNA patenting and technology transfer both prior to and since the NIH/cDNA filings. Our individual experiences encompass the academic, government, nonprofit, and industrial perspectives. On an individual basis, we have also participated in the international intellectual property debates. Our familiarity with the issues leads us to a clear consensus: this is a very complicated subject in which there are many legitimate points of view. We do believe that there is general agreement within the various communities about the necessity for developing therapeutic applications from publicly-funded research endeavors such as the Human Genome Project. In order to complete such research projects and to acquire information pertinent to developing new therapeutic applications, however, we also recognize that we must encourage the distribution of basic data.

We recognize the importance of the patent system and technology transfer in encouraging scientific publications and in developing and improving medical therapies. We strongly believe that creating useful new therapeutics is the public's ultimate goal, and we can find appropriate procedures to allow for data collection, dissemination, and development. Investment in new therapies will not happen without appropriate economic incentives; new therapies cannot happen without access to data. We recognize the symbiosis and tensions within and between these two realities. It is our position that the patent and technology transfer system can coincide harmoniously with ready access to information. Because the future of industrial development (not just in biology) depends on this synergy, it is incumbent upon us all to work together to ensure that the current patent system results in issuing thoughtful decisions. (Patent decisions do influence US participation in the global economy.)

It is also our concern that as companies and as members of the larger scientific community, we not overreact to the patent issues and consequent economic fears raised by the specific NIH/cDNA applications. (It is our perspective that the current patent system may well have the capability of handling issues raised by emerging uses of new technologies.) We believe that the current system, applied with rigorous standards for the definition of invention, is probably adequate for the emerging era of genetically-based science and product applications. In our opinion, **it could be quite detrimental for the US Congress to rush forward toward specific legislative remedies**. We propose a more modest approach of having many different experts work closely with the Patent and Trademark Office to develop internal policies to improve and enhance already-existing mechanisms for reviews and decisions. Additionally, we would also encourage continuing the global discussions on patent system harmonization. Improved synchronization of work-wide patent regulations for the purposes of increasing efficiency, simplifying the procedures, and reducing costs would be enormously beneficial to all involved[43]. [I added the bold face, not Darwin.]

Human Genome Sciences, Inc.

Address: 9620 Medical Center Drive
Suite 300
Rockville, MD 20850

Phone: 301-309-8504 or 310-251-6035
301-309-8513 fax

Founded: June 1992

President and CEO: William A. Haseltine

Director of Research and Development: Craig A. Rosen

Board of Directors: James H. Cavanaugh, James W. Church, Beverly Sills Greenough, Donald D. Johnston, George Poste (for Smith-Kline-Beecham), Joshua Ruch (for Everest Trust), Wallace Steinberg, Alan G. Walton, Harold R. Werner, and James Barnes Wyngaarden.

Haseltine was a professor at Harvard School of Public Health, where he has been a prominent AIDS researcher. He helped found Cambridge BioTech and Virus Research Institute, and is a consultant to or sits on the scientific advisory boards of several more biotechnology firms. Rosen was previously with Roche Institute of Molecular Biology. Cavanaugh has been President of HealthCare Investments Corp. since 1989 and participates in several of its partnerships. He previously served as President of SmithKline & French Laboratories (1981-1985), and serves on the board of 5 biotech and health care companies. Church retired from Johnson & Johnson in 1992, where he was President of Business Development, Pharmaceutical Sector. Beverly Sills Greenough is the former opera diva. Johnson retired from J&J in 1986, and is chairman of Osteotech. Poste is director of R&D for SKB, where he has worked since 1980. Ruch is an investment advisor to Everest Trust and CEO of Rho Management Co., Inc. Steinberg is Chairman of HealthCare Investments Corp., and serves on the board of three health care and biotechnology companies. He was formerly with J&J, and acted as CEO while HGSI was being formed. Walton is chairman or a member of several Oxford Bioscience Partnerships,

and serves on the boards of three biotechnology companies. Werner is Vice Chair of HealthCare Investments Corp. Wyngaarden is former NIH director, and also serves on the Board of Marion Merrill Dow Pharmaceutical Co. In the June 1992 agreement with TIGR, Venter was to be an HGSI Board member, but based on subsequent discussions with Venter, HGSI believes that part of the agreement no longer pertains. Dr. Venter confirmed it orally, and Bruce Cameron did so again via letter from TIGR[9].

Scientific Advisory Board: (Haseltine, chair), (Rosen), George F. Cahill (retired from Howard Hughes Medical Institute), Ronald W. Davis (Stanford), Michael Rosenblatt (Harvard Medical School), A. Ian Scott (Texas A&M), Thomas Waldman (NCI), and Stanley Falkow (Stanford).

Capitalization: Wallace Steinberg acted as CEO during 1992 and with Cavanaugh and Werner provided initial funding through HealthCare Investment Corp., which manages HealthCare Ventures, a series of limited partnerships based in Edison, NJ. Other partners include the Everest Trust (New York, NY), Oxford Bioscience Funds (Stamford, CT), and (through Everest) Aetna Casualty and Surety (Hartford, CT). The company started with a loan from and then a stock purchase agreement with HealthCare Ventures and Everest.

The Institute for Genomic Research (see description as a separate research center below) owned 21% of HGSI's stock, which was diluted to 4.3% by the public offering, and agreements from October 1992 and April 1993 specify that TIGR will receive $85 million from HGSI over 10 years (ending September 2002), of which $11 million had been paid by October 1993. This total comes from an initial payment schedule (p. 296)[25], augmented by an additional $1 million per year to bolster TIGR informatics (p. 356, item 9a)[32], and an HGSI buyout of over $1 million (over 3 years) in lieu of a TIGR grant application to DOE[33]. In return, HGSI retains intellectual property rights to the fruits of TIGR's work, except work conducted with government and nonprofit grant or contract funds. TIGR must consent before a majority interest in HSGI can be sold to a Japanese company.

SmithKline Beecham has entered a strategic alliance with HGSI. SKB paid $22 million by October 1993. Subsequent payments and stock purchases are contingent on HGSI attaining certain milestones. The first two milestones, for $12.5 million each, were already attained or soon will be. SKB is obligated to pay $16 million by August 1994 if it wishes to exercise certain international development and commercial rights. SKB also purchased $37 million in preferred stock shares under a May 1993 agreement, and is obligated to purchase an additional $25 million in shares when HGSI transfers tags for 90% of known expressed genes from the human genome or tags from 90,000 genes, whichever is smaller (payment is reduced to $20 million in shares if this milestone is achieved after May 1996). (This information is extracted from various sections of the prospectus for the initial public stock offering, mainly pages 28-29[34].)

The main agreement between SKB and HGSI is spelled out in a collaboration agreement that spells out the fields over which SKB exercises first right of refusal (p. 101), where HGS retains rights (p. 98), defines the milestones (p. 99), establishes a research committee to decide on items deserving further development at SKB (p. 109), and defines terms of confidentiality (p. 121ff)[29]. In aggregate, SKB appears to be obligated to pay up to $125 million, of which $22 million payment and $37 million stock were transferred at the outset ($59 million total), with another $25 million in direct payments subject to contingencies already met or soon to be met and side agreements with TIGR for a million or so per year (informatics) and one-time buy-out of a DOE grant of just over $1 million. SKB can terminate the agreement at any time before HGSI attains the 90%/90,000 gene milestone (p. 30)[34]. If terminated, product rights revert to HGSI, and SKB is obligated to purchase a pro rata share of outstanding stock based on progress toward that milestone.

HSGI has also entered into agreements with Plant Genome Sciences, Inc. and Industrial Genome Sciences, Inc., two firms owned by HealthCare Investment Corp. participants, many of whom helped to form HGSI [31; 28]. Plant Genome will develop and market agricultural and other plant applications, while Industrial Genome will do so for "all fields other than those

related to treatment, protection and diagnosis of, or products or processes to be administered to, humans, animals or plants" (p. 30)[34]. These might include industrial processing, environmental remediation, fermentation, etc. In return, these companies, if ever fully capitalized, would pay half of HGSI's obligated share to TIGR from the day they reach threshold capitalization. TIGR would also retain 21% stock interest in each of those companies should they become fully capitalized. These rights end in May 1995 if Plant Genome and Industrial Genome do not exercise them.

HGSI announced an initial public common stock offering on December 1, 1993, offering 2,250,000 shares, or 16% of total shares, for purchase by new investors. These were slated to raise an estimated $29 million if all options were exercised in full, which they were. The stock is now traded on the NASDAQ stock exchange. On December 28, 1993, the stock closed at $18.50 (or $42 million for the 2.25 million shares, less commissions and other fees). The 1993 stock high and low were $27.75 and $14.50 per share, respectively[3].

Research Plan: HGSI will own the patent and other intellectual property rights to TIGR's work. This is spelled out in an intellectual property agreement between TIGR and HGSI[27], and there are several relevant sections in an initial letter of agreement from Craig Venter to Wallace Steinberg, then acting CEO of HGSI (esp. items 9b, 10)[32] and the original research services agreement between HGSI and TIGR (esp. pp. 322-323)[25]. A separate intellectual property agreement governs HGSI-SKB. Each firm retains patents discovered by its employees, with a royalty scheme to allow cross-payments under the collaboration [29].

HGSI proposes to sequence human genes and those from other organisms. The first phase in this is the Expressed Sequence Tag method pioneered by J. Craig Venter at the National Institute of Neurological Disorders and Stroke (National Institutes of Health) and then at TIGR. The "genome scan" by ESTs will produce tens of thousands of gene tags, a rapid means of gene discovery. "When the Company discovers a gene which appears to have commercial value, the Company plans to isolate and sequence the full-length gene, express and purify the protein

encoded by the gene and assess its biochemical and biological activity (p. 20)"[34]. The ability to select appropriate targets for commercial development, based on preliminary analysis —presumably depending heavily on getting a first look and making predictions based on sequence information — will be a critical element.

HGSI promises to "apply for patent protection at each stage of the development process" (p. 20-21)[34]. This includes applying for patents when a gene has been partially sequenced (as an EST, for example) and later when the full cDNA sequence is known, and perhaps subsequently as new uses or specialized domains are discovered.

HGSI also explicitly plans to enter into collaborations with pharmaceutical and biotechnology firms, in addition to its agreement with SKB. The agreement cedes to SKB first rights to develop products in "human and animal health care, other than gene therapy (excluding gene therapy vaccines), antisense products and the use of genes for synthesizing drugs that were known at the time the Collaboration Agreement was executed [May 1993]" (p. 28)[34]. This includes "prediction, counseling, diagnosis, staging, vaccination, prophylaxis, treatment, and monitoring of human or animal (pre-and post-natal) disease states, disorders, phenotypes, and genotypes, forensic applications, devices for *in vitro* or *in vivo* human or animal health care applications, feed additives (but not feeds) for improving efficiency of feed utilization in non-human animals to improve growth of the animal or to improve the production of a substance naturally produced by the animal such as but not limited to meat from pigs, milk from cows, and eggs from chickens, diagnostic and therapeutic uses in sensor technologies, and related research and development and all medical information compilation services" (p. 100-101)[29]. SKB retains an exclusive worldwide license for products in this area, with certain exceptions that are blocked out in the SEC documents.

A research committee, half of whose members are appointed by SKB and half by HGSI, will approve those products to be targeted for development under the agreement. Dr. Haseltine clarified this clause at the January 7 OTA workshop, saying that the research committee will

review the results resulting from TIGR's work, but not all HGSI work. HGSI has extensive research efforts beyond preparing DNA for TIGR to sequence, and TIGR has an independent research board, so their efforts are by no means completely locked together and interdependent, despite the obvious connections. Tie votes on the research committee are to be resolved by negotiation or binding arbitration. HGSI has march-in rights if SKB decides not to pursue an approved product or if SKB terminates its development program, subject to royalties paid to SKB. SKB also retains a right to royalties on products outside the agreed area, if they are based on or incorporate patents or information generated by SKB, or products within the agreed area sold directly by HGSI or by a third party rather than SKB. HGSI retains all rights to products outside the SKB area of agreement (e.g., crop plants, fermentation techniques, or environmental remediation), subject to the previous caveat. HGSI "believes that it will identify a significant number of pharmaceutical candidates which SmithKline Beecham will not pursue, either because the project is not in a area of interest to SKB or because SKB, given its other commitments, chooses not to develop such products" (p. 29)[34].

HGSI has agreed to disclose all its technology to SKB (p. 29)[34]. SKB has a right to add gene therapy to the covered area if it acts before a deadline, but the prospectus does not state the deadline. HGSI will make at least 35 sequenators and 15 robotics machines available to SKB for use, if they are not necessary for projects approved by the research committee (p. 30)[34].

Comments on DNA patenting and technology transfer: The prospectus notes that "the Company's business would be enhanced if it were to obtain patent protection based on partial gene sequences, the Company does not believe its commercial success will be dependent upon its ability to do so" (p. 20)[34]. HGSI already has rights to whatever issues from patent applications filed on 9,900 partial gene sequences (p. 31)[34]. The patent application claims include the tag sequences, the full-length cDNA sequence, as well as products derived from those genes. The prospectus notes "a significant risk that patents will not be issued based on partial gene sequences ... [and] even if patents are issued on the basis of partial gene sequences, there may be

a great deal of uncertainty as to the scope of the coverage or protection provided by any such patents" (p. 31)[34]. HGSI had not yet filed applications for full-length genes that have been completely sequenced (p. 32)[34]. It notes that even if it does so, it may not have sufficient data to ensure that patents issue. HGSI also acknowledges that a patent issued for a partial sequence might undermine subsequent patents on the same gene. The prospectus also notes the potential for claims that inadvertently infringe on others' patents, as more companies and research groups undertake high-speed sequencing and gene identification.

Two of the patent applications were based on previous TIGR work supported by the US Department of Energy, and are thus subject to DOE's march-in rights and other government rights as may attach through executive orders, the Bayh-Dole Act and subsequent statutes and decisions (p. 8, 32)[34]. TIGR applied for another DOE grant to continue cDNA sequencing, but HGSI stepped in to buy that out, in order to avoid uncertainty about government patent and technology transfer constraints. HGSI agreed to pay TIGR $1,070,127 over 3 years, in return for which TIGR withdrew its DOE grant application (p. 47)[34; 33].

Finally, the company notes that it will protect some trade secrets, including a large proprietary database containing TIGR- and HGSI-identified genes. It has entered into confidentiality agreements with its employees, and TIGR has its own confidentiality agreements with its employees (pp. 32-33)[34]. Confidentiality clauses are present in the TIGR-HGSI and HGSI-SKB agreements, and in the employment and consultant agreements filed with SEC[26; 30]. These preclude disclosure to third parties of information, with certain exceptions, and in the case of consultant agreement, precludes taking notes other than for the company's benefit [26]. The TIGR confidentiality agreements focus on the 6-month period (extending to 18 months in some circumstances, when HGSI is actively pursuing a related project) during which it will refrain from public disclosure of sequence data (personal communication, Craig Venter, TIGR, January 5, 1994). Consultants and advisors for both firms will likewise be covered by confidentiality

agreements, and collaborators with either TIGR or HGSI must sign collaboration agreements with HGSI that include confidentiality clauses.

An agreement from 19 April 1993 stipulates that TIGR will not publish human cDNA sequences discovered before 1 April 1994 until October 1994, or 18 months after sequence disclosure to HGSI. TIGR can submit most sequences from its work to date for publication on 1 April 1994, and will be free to publish those come 1 October 1994[32]. The TIGR-HGSI agreement anticipates a publication entitled "Human Gene Anatomy" to be published on or after that date, edited by Dr. Venter and any collaborators. The later date, with longer confidentiality period, applies to sequences related to products under "active continuing programs" at HGSI (item 11)[32]. For cDNA sequences derived after 1 April, TIGR will not disclose them outside the company until 6 months after a US patent application is filed, or in the case of an item under active continuing programs at HGSI, 6 months after a foreign patent application is filed (which will, in general, be one year after filing the US application, for a total nondisclosure period of 18 months). If no patent applications are filed, TIGR may published after 6 months. These terms of an April 1993 letter replace an earlier, intellectual property agreement of 2 October 1992 [27; 32].

Incyte Pharmaceuticals, Inc.

Address: 3330 Hillview Avenue
Palo Alto, CA 94304

Phone: 415-855-0555
415-855-0572 fax

Founded: April 1991

President and CEO: Roy Whitfield

Director of Research and Development: Randal W. Scott

Board of Directors: (Whitfield), (Scott), Jeffrey J. Collinson (Chair), Frederick B. Craves, and Jon S. Saxe.

Whitfield was President of Ideon, a subsidiary of Invitron, and previously worked with Technicon Instruments and its predecessor CooperBiomedical, and before that worked with the Boston Consulting Group. Scott held senior positions in manufacturing and R&D at Invitron, and before that was senior scientist at Unigene Laboratories, a biotechnology company. Collinson is President of Schroder Venture Advisers, Inc. and was President of Schroder Venture Managers, Inc. from 1983-1990. He is also a director for Envirogen, Moorco, and Neurogen. Craves is Chairman of the Board of NeoRx Corp. and Microprobe Corp., both biotechnology companies. He was previously CEO and President of Berlex Biosciences owned by Schering AG, and before that CEO and President of Codon, a biotechnology company acquired by Schering in 1990. Saxe was President and CEO of Synergen 1989-1993, and before that was Vice President Licensing and Corporate Development for Hoffmann-La Roche, Inc. He was head of patent law at Hoffmann-La Roche for 11 years before that. He also serves on the boards of InSite Vision, Inc., and Protein Design Labs, Inc.

Scientific Advisory Board: Charles R. Cantor (Boston University), Charles J. Fisher, Jr. (Cleveland Clinic Foundation/Case Western Reserve), Gerald Gleich (Mayo), Ralph Snyderman

(Duke), Burton Sobel (Washington University), A. D. Strosberg (Institut Cochin de Genetique Moleculaire, Paris), and Steven J. Weiss (University of Michigan).

Capitalization: Incyte began operating in August 1991, upon acquiring parts of Invitron Corp. Its scientific staff largely derives from Invitron and its subsidiary, Ideon. Incyte was launched with a collaborative agreement on Bactericidal/Permeability Increasing protein (BPI), under contract with Genentech. This agreement was terminated in March 1993[38]. All the company's revenues through October 1993 came from this contract. Incyte also has collaborations with Mayo clinic and a September 1992 agreement with Ciba-Geigy that resulted from a patent interference proceeding, resolved in January 1993[36; 40; 37].

In November 1993, Incyte announced the sale of 2,000,000 shares of stock, or 31% of its total shares, for new investors, hoping to raise $16 million[41]. The initial public offering netted $17.25 million for Incyte from the sale of 2,300,000 shares, including an over-allotment by its underwriter, D. Blech & Co (New York, NY)[39]. There are now 6,385,000 shares of stock outstanding. It is traded on the American Stock Exchange as IPI, listed in papers as Incyte. On December 28, the stock closed at $9.125, or $18 million for the 2 million shares, less commissions and other fees. The 1993 stock high and low were $11.875 and $7.50 per share, respectively[1].

Research Plan: Incyte's current research plan evolved out of seven years of research by its scientists. It is based on high speed sequencing to identify genes and their corresponding proteins. Incyte's Database Discovery approach is based on comparing new protein or DNA sequence to known genes and protein sequences. It is sequencing "thousands of partial genes per month" (p. 20)[41]. It then "uses computer analysis to determine whether the sequence has potential pharmaceutical utility." Incyte has "already sequenced thousands of partial genes from various cells and tissues, including certain white blood cells in their resting and activated states as well as from a human mast cell tumor line for which the Company has an exclusive license from the Mayo Clinic" (p. 20)[41]. As of June 30, Incyte had performed partial sequences on

20,000 cDNA templates (p. 22)[41]. Dr. Randal Scott cited the figure of 50,000 partial cDNA sequences at the January 7, 1994 workshop, with an anticipated 150,000 more over the next year or so. This is corroborated by a recent background statement from the company notes that "as many as 12,000 unique genes" have been found among the 50,000 DNA templates sequenced. It expects to have exceeded 200,000 sequenced templates by the end of 1994, and "within two years it will have partial sequences for nearly all of the estimated 100,000 genes of the human genome"[42].

Based on the partial gene sequences, the company intends to "identify and isolate selected full cDNA sequences with potential therapeutic applications for further development" (p. 23)[41]. Incyte is focusing its effort on cDNAs derived from mRNA transcripts of cells in defined states — for example activated macrophages, cancer cells, or "disease-state" cells. This starts by finding the relative prevalence of transcripts, focusing on those whose expression rises markedly with the change in state. Incyte also expects to establish collaborations that would help pharmaceutical firms identify drug targets, and also to look for changes in gene expression before and after drug treatment, for clues about mechanism and further drug targets. Incyte's goal, like that of TIGR and HGSI, is to create a commercial database of genes correlated to tissue types, disease states, developmental stages, and organ specificity [42]. This general similarity no doubt obscures important technical differences, but those specifics are proprietary.

As full-length cDNA sequences are obtained from interesting EST candidates, they will be amplified and their protein products characterized for biological activity. Selection of targets will largely be based on sequence similarity to known genes and proteins, and changes in expression with known states. In addition to sequence tag-cDNA-gene product characterization, the company also intends to collaborate with firms that possess inhibitors of the protein functions encoded by Incyte-identified genes.

Incyte intends to "form collaborations with pharmaceutical, gene delivery, and drug screening companies covering either gene sequences associated with functional classes of

proteins or other pharmaceutical applications of the Company's Database Discovery approach" (p. 20)[41].

Comments on DNA patenting and technology transfer: Incyte holds three US patents to the Bacterial Permeability-Increasing protein (BPI)[74]. This is a bactericidal protein that it was developing for therapeutic purposes under an agreement with Genentech from 1991 to March 1993, when the agreement was terminated with Incyte retaining the intellectual property and marketing rights, subject to a royalty payment to Genentech[38]. Incyte expects to begin clinical testing on this or one of its other two protein products undergoing preclinical testing as lead compounds. BPI was discovered by a process similar to that it intends to pursue for the entire human genome. The other two, Protease Nexin-1 (the one that was subject of interference proceedings with Ciba-Geigy) and Galaptin 14-1, were discovered by protein biochemistry. BPI is under preclinical investigation for treatment of sepsis, endotoxemia, and Adult Respiratory Distress Syndrome; Protease Nexin-1 for osteoarthritis and inflammation; and Galaptin 14-1 for transplantation rejection and multiple sclerosis. Incyte expects to begin clinical testing of one of these three, or a derivative of them, in the next two years.

As of July 1991, Incyte had filed approximately 100 patent applications pertaining to 20 protein molecules, and was "exclusive licensee to a number of other patent applications" (p. 27)[41]. In addition to the 3 US patents for BPI, Incyte holds 7 US and 1 Australian Protease Nexin-1 patents, and 1 European, 1 French, and 2 Australian patents related to Galaptin L-14-1, and 2 additional US patents for Human Defensin HNP-4. These patents include sequence data. The remaining patent applications are pending. No foreign applications have yet been published. Incyte does not state how many partial cDNAs are included in the patent applications, nor discuss the scope of its claims. It does however, state that "Incyte is considering each sequence on its merits for filing under the PCT or directly in national patent offices" [61]. The company states it will also rely on unpatented trade secrets and "has taken security measures to protect its data and is in the process of exploring ways to further enhance the security for its data" (p. 28)[41].

Incyte "has discovered a wide variety of novel cDNA compounds. Patents on each must be given the scope warranted by the disclosure and prior art. Incyte believes the patent office will recognize that these are unique compounds and that the appropriate legal standards of patentability will be applied"[61].

At the January 7, 1994 OTA workshop, Randal Scott announced that Incyte had partial sequences from 50,000 cDNAs, and expected to reach 150,000 more in the next two years. He told me that the corporate strategy is to file patent applications for each 5,000 EST sequences, but to keep claims relatively circumscribed. The philosophy is to file continuations in part on full-length cDNAs as they are further characterized. The kilopatents (my coinage, not his, referring to the applications that cover 5,000 ESTs each) are intended to establish a filing date and priority of invention for the genes that are later more fully characterized. The company states that "these patent applications are fully supported with utility an include many sequences which Incyte believes to be novel and unobvious"[61]. At the workshop, Scott did not believe that Incyte's strategy hinged on success in obtaining patent protection for ESTs, but rather depended on establishing invention with an early filing date and then rapid pursuit of leads that promise definite utility. He did not tell me, and I did not ask, how many of the 50,000 EST sequences are covered by the patent applications filed to date, and this was not clarified in the company's reply letter; presumably the omission was deliberate.

The letter from Incyte accompanying their corrections and comments included a paragraph the corporate officers believed should be relayed to OTA about DNA patenting:

> Patent protection on commercially relevant cDNAs is essential to the success of the biotechnology and pharmaceutical industries. The PTO's ultimate policy on gene fragments must not obviate or preclude coverage on full length cDNAs, nor should patent protection for new molecules be denied based on the method discovery, "high-throughput" or otherwise. With Incyte's commercialization strategies, securing rights to these new molecules is important not only to Incyte but to the numerous pharmaceutical and biotechnology company collaborators[61].

Mercator Genetics, Inc.

Address: 4040 Campbell Avenue
Menlo Park, Ca 94025

Phone: 415-617-0880
415-617-0883 fax

Founded: Spring 1992

President and CEO: Kathy Behrens (acting)

Director of Research and Development: Dennis Drayna

Founders: David R. Cox (Stanford), Dennis Drayna, formerly of Genentech, and Richard M. Myers (Stanford)

Scientific Advisory Board: J Michael Bishop (UC San Francisco), Eric D. Green (Washington University), Gerald Rubin (UC Berkeley), and William S. Sly (St. Louis University).

Capitalization: Started with funds from venture capital arm of Robertson, Stephens & Company, amount not specified, but "sufficient to comfortably complete its first year or more of operations and move into permanent research facilities in Northern California."

Research Plan: Mercator combines a very strong group of scientific founders with an impressive group of scientific advisors. The objective of the company is to develop therapeutics for common diseases by obtaining the genes contributing to them before anyone else. The company expects to be first to find disease-related genes by using "a series of proprietary technologies" that are not specified[50]. The conceptual approach is positional cloning, or "reverse genetics." Mercator will thus move from genetic linkage to physical maps, based on YAC collections available to it, to physical maps in smaller fragments (BACs, cosmids, or P1 clones) intermediate in size between YACs and fragments that can be sequenced directly.

Identifying the genes will entail cDNA screening, mutation detection, and high speed DNA sequencing. Mercator promises to reduce the number and increase the speed at several steps in this process. Mercator started with a list of 50 disease-related genes as potential targets, and has narrowed that list to 5-7 candidates which will be further refined to 3-5 projects.

Mercator is clearly banking on the scientific strength of its founders. Drayna was prominent in the hunt for the gene predisposing to Werner's syndrome, and Myers and Cox were heads of the UCSF genome center that moved to Stanford. Both have long been associated with technical advances in genome research, Cox most strongly associated with radiation hybrid mapping and Myers with denaturing gel electrophoresis.

Comments on DNA patenting and technology transfer: The public information document from Mercator states only that "details of Mercator's technical strategy is [sic] being reduced to patent applications and practice"[50].

Millennium Pharmaceuticals, Inc.

Address: 640 Memorial Drive
Fifth Floor
Cambridge, MA 02139

Phone: 617-374-9480
617-374-9379 fax

Founded: January 1993

President and CEO: Mark Levin (acting); Sherry L. Reynolds, Business Development Consultant

Director of Research and Development: not noted in literature or articles, but 42 employees hired[71; 62].

Board of Directors: Not listed. Levin is a partner in the Mayfield Fund and was founding CEO of Cell Genesys, CytoTherapeutics, Focal, and Tularik, all biotechnology companies. He has also worked for Eli Lilly, Miller Brewing, and Genentech. Sherry Reynolds is a consultant who has worked with Glaxo, Sphinx, and Genesis. In addition to Mark Levin, the Board of Directors includes Raju Kucherlapati, Ph.D. of Albert Einstein; Grant Hendrick, a partner at Mayfield; Hell Helman, a partner at Greylock; John Deer, a partner of Kleiner, Perkins, Caufield and Byers; and Eric Lander, Ph.D. of the Whitehead Institute for Biomedical Research and MIT.

Founding scientific advisors: Daniel Cohen (CEPH/Foundation Jean Dausset), Jeffrey Friedman (HHMI/Rockefeller University), and Eric Lander (MIT/Whitehead Institute).

Scientific Advisory Board: David Baltimore (Rockefeller University), Graeme Bell (University of Chicago), Patrick Brown (Stanford, soon UCLA), Neal Copeland (NCI), William Gilbert (Whitehead Institute), Nancy Jenkins (NCI), Rudolph Leibel (Rockefeller), Harvey Lodish (MIT/Whitehead), Kenneth Polorski (University of Chicago), Jeffrey Ravetch (Memorial

Sloan Kettering), Bento Soares (Columbia), David Valle (Johns Hopkins), and Richard Wilson (Washington University).

Capitalization: Millennium received $8.45 million in initial funding from an investment consortium led by the Mayfield Fund[5; 2; 20; 52; 53; 71; 76]. Investors listed are: Mayfield fund; Kleiner, Perkins, Caufield & Byers; Greylock Management Corp.; Venrock Associates; Sofinnova, Inc.; CW Group; PaineWebber; and David Goeddel[52].

Research Plan: The publicly available data about Millennium are quite sketchy. Press accounts have focused almost exclusively on the scientific founders or the $8.45 million venture funding, but very little on the research plan or operation of the firm. Millennium's strategy is to isolate disease-related genes for polygenic and multifactorial disorders and use those genes to target drug development. Three classes of disorders are noted among the initial areas of interest: obesity, Type II (late onset, non-insulin dependent) diabetes mellitus, and immune dysfunction.

Millennium just moved to a new 48,000 square foot facility in Cambridge. Millennium promises to build an infrastructure to enable large scale genotyping (for linkage analysis), YAC isolation and other physical mapping techniques, cDNA analysis, and DNA sequencing. It will pursue human and animal models of human disorders, and collect human families for genetic linkage analysis. One appealing aspect of Millennium's business plan is its exclusive rights to develop genome mismatch scanning.

Genome mismatch scanning is potentially a powerful new approach to genetic linkage mapping. It relies on selecting for DNA stretches that are identical between two individuals. It is used to map regions that are identical between two related individuals. Genomic DNA is taken from both individuals, and cleaved into fragments suitable for hybridization in solution (up to 20 kilobases). One individual's DNA is methylated and the other's is not. DNA from the two individuals is combined, and binds together. Roughly half of the resulting hybrids are hemimethylated (methylated on only one strand and thus comprised of one strand from each

individual). The other half are either fully methylated or not at all, thus arising entirely from one individual or the other. Fully methylated and unmethylated DNA is cleaved, leaving smaller fragments with blunt-ended double-stranded DNA at the cleavage site, and only hemimethylated hybrids of full length. The full-length hemimethylated hybrids have 3' overhangs, which are not subject to digestion by the enzyme subsequently used. Some of these remaining full-length hybrids will contain single-base or short stretches of internal mismatches, indicating areas where sequences are slightly different. These areas are detected by bacterial DNA repair enzymes that introduce a single strand nick. The molecules containing nicks and all blunt-ended DNAs are digested, leaving only areas of full homology — stretches that are identical-by-descent. These DNA fragments can be used to generate probes, and mapped back to the genome to look for areas of identity-by-descent in the two individuals. This back-mapping can be done by *in situ* hybridization, or in the future by probing ordered clone sets derived from physical maps of genomic DNA.

This capacity means that one can find areas of common inheritance between two relatives both of whom have a specific trait, for example a genetic disease. The linkage analysis can proceed by analysis of identity-by-descent rather than relying on recombinations and large pedigrees with many affected relatives. The strategy becomes one of finding many pairs of affected relatives and looking for common areas of identity-by-descent. This is particularly appealing for disease susceptibility genes, low penetrance disorders, and conditions with late onset. It is also attractive for finding multiple shared regions that may be associated with polygenic disorders. Calculations suggest that as few as 10 grandparent-grandchild pairs or 6 first cousin pairs might be sufficient to detect rare monogenic disorders[58].

The technique also seems likely, with some tweaking, to be useful for homozygosity mapping, something Botstein and Lander wrote about several years ago[48]. This is another inheritance-by-descent technique that quickly reduces the number of affected individuals needed to find regions containing rare recessive alleles. With other modifications that take advantage of

the steps that detect short deletions and single-base mismatches, genome mismatch scanning might also be useful to quickly look for wild type-mutant differences among regions containing candidate genes, and for other purposes. (These are my own speculations, not Brown's or Millennium's.)

If one needs higher resolution with conventional markers, one currently needs to find either more informative markers or genotype more family members. With genome mismatch scanning, the prospects seem bright that sufficient numbers of markers will be completely informative to enable higher resolution by adding markers rather than family members. The technique is a very powerful, highly conducive to automation, and holds great promise for rapid genome linkage analysis. Its applicability to humans, however, is only now being tested.

The scientific strengths that appear most distinctive to Millennium are its experience with genome research on a large scale (through Cohen's affiliation with CEPH/Genethon and Lander's Genome Research Center), its broad base of technologies, and its access to and past study of mouse model disorders and associated mutations. The company claims proprietary technologies for the identification of disease-related genes. Its investors have ample experience with other biotechnology and pharmaceutical ventures. Millennium shares some common therapeutic targets with Sequana, and Sequana has also forged links to the Jackson Laboratories to secure rights to mouse strains affected with obesity and models of non-insulin dependent diabetes.

Comments on DNA patenting and technology transfer: Millennium holds an exclusive license from Stanford to develop Genome Mismatch Scanning for therapeutic purposes. The technique was developed in the laboratory of Patrick Brown, one of the company's scientific advisors. This is an important feature of its strategy. Millennium's exclusive license for therapeutic purposes is distinct from nonexclusive licenses given to several firms for diagnostic and research purposes, including at least Collaborative Research and Myriad Genetics.

Millennium's fact sheet refers to "proprietary technologies," in the plural, implying additional trade secrets or pending patent applications on which the company's literature is silent. I found no public statements from Millennium about cDNA patenting or other aspects of technology transfer or patent law.

Myriad Genetics, Inc.

Address: 421 Wakara Way
Suite 201
Salt Lake City, UT 84108

Phone: 801-582-3400
fax 801-584-3640

Founded: May 1991 (Helix Technologies was incorporated in Utah then. Myriad Genetics became the successor company under the Delaware corporate charter in November 1992)

President and CEO: Peter Meldrum

Vice President of Research: Mark H. Skolnick (University of Utah)

Vice Chairman of the Board: Walter Gilbert (Harvard University)

Director, Myriad Diagnostic Services, Inc.: Wayne C. Patterson

Board of Directors: John J. Horan (former chairman, Merck & Co.); Dennis B. Farrar (Chairman, Founder's Fund); Arthur H. Hayes, Jr. (former commissioner, FDA); Kevin B. Kimberlin (Chairman, Spencer Trask Securities and former founder of Immune Response Corp.); and Dale A. Stringfellow (President and CEO of Celtrix Pharmaceuticals, Inc. and former VP, Preclincal Cancer Research at Bristol-Myers Squibb)

Scientific Advisory Board: R. E. Keith Fournier (Fred Hutchinson Cancer Research Center); Gilbert Omenn (Dean, School of Public Health, University of Washington, Seattle); Jasper D. Rine (Director, Human Genome Center, Lawrence Berkeley Laboratory and UC Berkeley); Robert R. Williams (University of Utah); and Barbara Wold (Caltech, also chairman of NIH Human Genome study section)

Capitalization: The company has raised $11.3 million from private financing[57]. Eli Lilly & Co. holds a $1 million equity share in Myriad, and also is pledged to pay $1.8 million over three years, starting August 1992 (p. 12)[56], and an additional $1.2 million in milestone payments[66].

Research Plan: Myriad's fact sheet states that its "near-term commercial goal is to develop diagnostic tests based on patented predisposing disease genes. Myriad plans to initially form strategic alliances with established pharmaceutical companies for development and marketing of therapeutic products based on its proprietary genes. Longer term, Myriad plans to develop therapeutic products independently"[57]. Myriad promises to use "a unique gene discovery strategy combining genetic information with advanced gene mapping and DNA sequencing technologies, enabling the Company to rapidly map and isolate important, disease-causing genes." One of its distinctive attributes is association with the University of Utah's genealogical database on 1.5 million descendants and 200,000 families of Utah's 10,000 early pioneers, the so-called Mormon pedigrees. More than $50 million in federal funds have gone into developing this database (p. 11)[56; 66].

It is clear from the corporate plan that Myriad will focus on cancer genetics, cardiac disease, and other major disorders associated with genes. Its approach is positional cloning, and its edge will derive from exclusive access to the Mormon pedigrees, extensive clinical expertise at the University of Utah, informatics and genetic linkage methods based on Utah's genetic epidemiology program, and such proprietary technologies as Skolnick, Gilbert, Williams, and others bring to the firm. A final unique aspect of Myriad is its worldwide exclusive license to Dr. Keith Fournier's subtractive hybridization technique developed at the Fred Hutchinson Cancer Research Center, University of Washington, Seattle.

The company's literature relies heavily on the scientific backgrounds of co-founders Mark Skolnick and Walter Gilbert. Skolnick is a genetic epidemiologist who was third author on the

landmark 1980 RFLP paper[7]. It was an April 1978 presentation on genetic linkage between HLA and hemochromatosis by one of Skolnick's graduate students, Kerry Kravitz, that led Botstein and Davis to think seriously about a global human RFLP map. Skolnick has long worked on the genetics of multiple genes associated with various cancers. Nobel laureate Gilbert was a co-founder of Biogen[21], co-discoverer of the Maxam-Gilbert DNA sequencing technique[49], and an early spear-carrier for the human genome project.

Myriad's initial focus is on melanoma, breast cancer, prostate cancer, colon cancer, and lung cancers. Myriad is also interested in hypertension, heart disease, obesity, and stroke[66]. The company plans to launch a diagnostic test this year, 1994.

Myriad has formal exclusive alliances with the Center for Cancer Genetic Epidemiology and the Cardiovascular Genetics Research Clinic at the University of Utah in Salt Late City. In August 1992, Myriad signed a three-year collaborative agreement with Eli Lilly & Co. and its subsidiary, Hybritech, Inc. This focuses on finding and sequencing "the gene" predisposing to breast cancer. Myriad has been in the hunt for the melanoma gene on chromosome 9, and the 17q BRCA1 gene. It will retain testing service rights for the breast cancer gene (assuming it finds it first), and has formed Myriad Diagnostic Services, Inc. to develop and market tests for this and other major conditions.

Comments on DNA patenting and technology transfer: Myriad clearly intends to hunt for and patent human genes associated with disorders of high prevalence. The company is taking advantage of its unique access to the Mormon pedigrees, clinical resources at the University of Utah, and exclusive licenses for subtractive hybridization and prohibitin patents. The strategy will depend on identifying genes before others and protecting them by patent. Terms of intellectual property agreement with the University of Utah grant the company exclusive, world-wide rights[66]. The Federal Government, through NIH support for the Mormon pedigrees, has a nonexclusive license for its own use but not for any commercial applications[66]. The company's description does not mention any relevant NIH, DOE, or other grants, particularly the

relationship between Dr. Skolnick's or Dr. Gilbert's grant-funded research and the Company's intellectual property rights. If such agreements exist, they would presumably have been negotiated with Myriad by the technology transfer and licensing offices of Harvard and the University of Utah.

Under the Lilly agreement, Myriad retains diagnostic testing *service* rights for the breast cancer gene, while Lilly and Hybritech have commercial rights to therapy and diagnostic *products*. Myriad will receive royalties on any therapeutic or diagnostic products developed under the agreement (p. 12)[56].Myriad also has exclusive worldwide rights to the Fred Hutchinson Cancer Research Center's (Seattle) subtractive hybridization technique, having filed US and foreign patent applications on behalf (and in the name) of the Center. (This patent was published in Europe under the PCT, as WO93/5149, and is listed among those taken from the BioWorld Compendium submitted separately.) Myriad has exclusive US rights on prohibitin, a protein found mutated in some breast cancers, licensed from NIH (p. 12)[56]. Myriad licensed an hypertension-associated gene on August 4, 1993, from INSERM and the University of Utah[57; 66].

Myriad has a license to Stanford's genome mismatch scanning technique (signed 9/1/93), for gene discovery and diagnostics *in vitro* use[57; 66]. Millennium's exclusive world-wide license for genome mismatch scanning is for therapeutic commercial applications *in vivo*.

Sequana Therapeutics, Inc.

Address: 11099 North Torrey Pines Road
Suite 160
La Jolla, CA 92037

Phone: 619-452-6550
619-452-6653 fax

Founded: January 1993

Chairman and CEO: Kevin J. Kinsella

Vice President of Research and Development: Timothy J. R. Harris (former director of biotechnology for Glaxo Group Research and before that with Celltech)

Management: (Kinsella), Ivor Royston, director (Forward Ventures, former founder of Hybritech, IDEC, and GeneSys Therapeutics); Carlos Zamudio (bioinformatics); M. Scott Salka (business operations), Jay B. Lichter (genetics)

Scientific Advisory Board: Peter Goodfellow (Cambridge University, UK); Hans Lehrach (Imperial Cancer Research Fund, London); Anthony Monaco (Oxford University, UK); John A. Todd (Oxford); David E. Housman (MIT); Stephan Guttmann (former senior VP, Sandoz Pharma, Ltd.), Allan Bradley (Baylor); Alan J. Buckler (Massachusetts General Hospital); Mark Boguski (National Center for Biotechnology Information, National Library of Medicine);Burton Christensen (former Senior VP, Merck, Sharpe & Dohme Research Laboratories)

Capitalization: First round funding of "under $5 million" came from Avalon Medical Partners, of which Kinsella is managing partner[4]. Second round financing produced $12 million [47]. It is, at this point, a privately held startup company.

Research Plan: Sequana's focus is on positional cloning to identify and isolate disease-associated genes or other genes of interest (e.g., those associated with baldness). Through its scientific advisory board, it taps expertise that has been associated with many successful gene

hunts: testis-determining factor (Goodfellow), Duchenne/Becker muscular dystrophy (Monaco), Wilm's tumor and multi-drug resistance in humans and mice, melanoma and neuroblastoma (Housman), and Huntington's disease and Wilm's tumor (Buckler). The scientific advisors also bring expertise in computation (Boguski); physical mapping and informatics (Lehrach); genetics of diabetes mellitus (Todd); transgenic "knockout" mice (Bradley); and medicinal chemistry and drug discovery (Guttmann, who developed industrial synthesis of oxytocin, bradykinin, calcitonin, and corticotropin analogues and helped with many other projects at Sandoz; and Christensen, who holds 180 patents and directed the Frosst Laboratories for Merck in Canada, and was a principal in developing cefoxitin, imipenem, ivermectin, H. flu vaccines, and finasteride).

Sequana plans to address polygenic complex disorders, especially obesity, diabetes mellitus, and osteoporosis. These are all highly prevalent conditions with demonstrable genetic contributions arising from genes that have not yet been identified, with the very recent exception of a gene for osteoporosis (January 1994, at NIH). Sequana's literature stresses the prowess of its scientific advisors, signaling its intention to use positional cloning as a means to hunt down disease-associated genes before others, and to protect those with patents or other intellectual property protections.

Sequana expects to begin clinical testing of diagnostics in the next two to three years, and then hopes to move into clinical testing for therapeutics in five years[4]. The company has formed a collaboration with Jackson Laboratory to focus on type II (non-insulin dependent, or adult-onset) diabetes mellitus[8; 46; 67; 75]. This collaboration is expected to elucidate non-insulin dependent diabetes and also to help explain obesity by taking advantage of *tubby* and other strains of mice held by the Jackson Laboratory. To move forward on osteoporosis (and perhaps eventually hypertension and other cardiovascular disorders), Sequana struck up an agreement with the Southwest Foundation for Biomedical Research (San Antonio, TX). The Foundation houses baboon colonies, containing 3,000 baboons. Of those, 2,000 baboons have been

pedigreed, and some pedigrees appear to have a familial condition that models osteoporosis[64; 69]. Sequana announced a collaboration with another firm, Alopex, to find genes associated with baldness, hirsutism, excessively long hair growth, and other hair conditions[65; 68]. This will involve study of the mouse strain containing the *angora* mutation which produces excessive hair length (which might be of interest to sheep breeders and other agricultural interests), and mouse and human pedigrees that demonstrate familial baldness.

Comments on DNA patenting and technology transfer: Sequana has not issued public policy statements on patent law or technology transfer. Its corporate strategy clearly involves some private entities (Alopex), but also publicly funded institutions that receive federal grants, and are thus reliant on the Bayh-Dole and other statutes to secure and license patent rights. Sequana's strategy is to focus on high prevalence conditions with known genetic contribution, isolate genes by positional cloning, and protect those genes for diagnostic and ultimately therapeutic development. The strategy relies on getting there first. Sequana is focusing on diabetes and obesity, baldness and hair conditions, and skeletal conditions. Only Millennium overlaps with these interests, with diabetes and obesity among its interests. The scientists associated with Millennium also collaborate with Jackson Laboratories through the Boston-based, NCHGR-funded genome research center. Myriad and Collaborative Research are focusing on cancer. Several of the companies include hypertension and atherosclerosis among their targets.

Sequana appears to be relying on the scientific expertise of its advisors and employees to enable it to find and fence off genes before other university or corporate groups do so, or it will license from the university groups that cross the line first. It thus will rely on both technology transfer and patent law to secure patent protection.

CEO Kevin Kinsella's comments on the NIH patent application, and subsequent applications for only partially characterized gene sequences of unknown function, is consonant with the statements made at the January 7 OTA workshop. He did not support the extensive

claims to full length genes and resultant products from the partial gene sequences. He believed that the Patent and Trademark Office was likely to reject those patents, but was strongly supportive of the general notion of patenting genes whose function is known and for which specific applications can be foreseen. He noted that *Manson* decision should be taken seriously, and endorsed its spirit — that intermediate products and research tools should not be locked up prematurely, but should be patentable only when a specified utility beyond research has been identified.

The Institute for Genomic Research

Address: 932 Clopper Road
Gaithersburg, MD 20878
TIGR plans to move to another facility in about a year

Phone: 301-869-9056
301-977-7286 or 301-869-9423 fax

info@tigr.org

Founded: June 1992

Director: J. Craig Venter

Board of Trustees: (Venter, chair), Rita R. Colwell (invited, pending; University of Maryland); Theodore N. Danforth (Long Island, NY); Mary-Claire King (UC Berkeley), Jack B. McConnell (Hilton Head Island, SC); Leslie Platt (COO of TIGR), and Martin Rodbell (former R&D director for NIEHS)

Scientific Advisory Board: (Rodbell, chair); W. French Anderson (University of Southern California); Darrell Doyle (SUNY Buffalo); Hamilton O. Smith (Johns Hopkins Medical School); Chris Somerville (Stanford), and Carl Woese (University of Illinois)

Funding: $11 million 1993 funds under an agreement with Human Genome Sciences, Inc., with commitments for another $74 million through September 2002, when the agreement ends[34]. The payments are spread over the 10-years in graduated payments (to be paid each year in quarterly installments). In the schedule initially agreed to between TIGR and HGSI, annual payment rises from an initial $950,000 at time of initial agreement to $7,500,000 in years 4 and 5, and then gradually drops to $5,350,000 in year 10 (p. 296)[25]. This schedule was modified by a later agreement, increasing the annual amounts overall by adding $1 million a year for informatics[32], plus the extra payment for buy-out of the DOE grant application in 1993-1995[33]. TIGR also retains 4.3 percent of the stock of HGSI and similar fractions of PGSI and IGSI (21

percent before public offering dilutes this). For further details, see the section under Human Genome Sciences, Inc.

Research Plan: TIGR is dedicated to employing DNA sequence technology and informatics to rapid analysis of DNA from the human and other genomes. As of December 1993, TIGR had 97 employees, including 84 scientists and technicians[34]. TIGR is, in essence, an autonomous research institute whose funding will derive from connection to the for-profit Human Genome Sciences, Inc., which in turn will reach agreements with other firms (most notable, SmithKline Beecham, or SKB, to date) and may also pursue products itself. Some parts of the funding to be paid by HGSI will be shifted to Plant Genome Sciences, Inc., and Industrial Genome Sciences, Inc., derived from their focus on agricultural and non-pharmaceutical, non-agricultural applications, respectively, if they become fully capitalized. (To date, intellectual property agreements have been signed.[31; 28]) The main guarantor of continued TIGR funding now is the HGSI agreement with SKB. The basic tit-for-tat is an exchange of expertise and intellectual property rights to HGSI (plus PGSI and IGSI), which in turn gets funding from SKB through their strategic alliance (in addition to HGSI's public offering). For purposes of business development, TIGR is part of a front-end of drug discovery and other applications of gene discovery, linked to HGSI, IGSI, and PGSI by intellectual property, equity, and financial ties.

TIGR's scientific interests are not, however, entirely constrained by ties to its industrial sponsors. It has an independent Board of Trustees and Scientific Advisory Council, although some members also have ties to some individuals involved in HGSI or the parent partnerships (mainly HealthCare Investment Corp.) that spawned both TIGR and HGSI. TIGR's stream of funding obviously depends to some extent on the success of the companies that fund it, and its equity holdings in those companies reinforce that bond, but its funding for ten years is largely assured by the SKB agreement. The last word on TIGR's scientific interests is best left to its own description, taken from the new January 1994 brochure:

> The Institute for Genomic Research is a not-for-profit research center devoted to accelerating the understanding of human evolution by the sequencing, mapping and

functional characterization of human, animal, and plant genomes. The Institute brings scientists together in a collaborative environment to identify and characterize novel genes and gene families through the application of DNA sequence analysis, computational biology, gene expression, model organism studies, and comparative evolutionary biology. Departmental research in the Institute is supported by a large-scale DNA sequencing facility with state-of-the-art robotics and informatics.

With the original strategy proposed for the Human Genome Project, it was predicted that the sequence analysis of all human genes would be completed early in the next century. TIGR anticipates that over 50% of human genes will be identified and at least partially sequenced during 1994. This will change the focus of international human gene research from DNA sequencing to characterization of the biological function of genes.

During the past year, TIGR has implemented a new strategy to understand biology, using the expression patterns of thousands of genes to understand human development and physiology at the molecular level. The knowledge gained from this research can be expected to lead to the identification of genes associated with many diseases, to facilitate early diagnosis of some cancers, and to help lead to new therapies. TIGR's high throughput human gene sequencing is also leading to the identification of novel proteins that are involved in physiological processes such as cell signaling, cell growth and differentiation, immune responsiveness, and aging[72].

Comments on DNA patenting and technology transfer: Craig Venter, speaking for TIGR, has the most fully articulated public position on patenting genes and gene fragments of any institution or company surveyed, in large part because he testified before Congress on the question in September 1992. He had just left government employ and spoke as the director of the newly formed TIGR, just beginning to show its stripes.

In that testimony, Venter strongly supported the idea of patenting individual genes for diagnostic and therapeutic purposes, and gave the two principal rationales for NIH's previously seeking patents for 6,000 Expressed Sequence Tags developed in his NINDS intramural laboratory, explaining that the purpose was to generate public discussion and to forestall loss of patentability of full-length genes which could be caused by the deposit of partial cDNA sequences in the public domain. The argument for protection of future patentability turns on the argument that "No gene is obvious a priori. However, the publication of a partial sequence of a human gene may render the sequence of the complete gene obvious to a worker of ordinary skill in biotechnology. Standard methods exist for obtaining the complete clone and sequence of a

gene given a partial sequence of the length typical for EST sequences" (p. 62)[78]. The corollary possibility was that the Patent and Trademark Office (and the US courts) could interpret obviousness so that "if publication of partial sequences without patent protection can block patenting of complete genes and products based on them, then the US biotechnology industry is in grave risk of being irreparably damaged by publication of the results of the Human Genome Project, whether these results are obtained in the US or abroad" (p. 62)[78].

Given this rationale, the NIH decision to abandon its applications means this threat may be tested. This position must have changed, as Dr. Venter theoretically had (untested) rights to march in when NIH abandoned its application, as the inventor. Venter agreed to this in advance of NIH Director Harold Varmus's decision, and that stance is at first blush somewhat puzzling, if it leaves the 6,000 ESTs "naked," rendering the genes that contain them unpatentable. One can only speculate that the risk-benefit calculations included an assessment of the considerable political costs of taking what would surely be seen as a highly unpopular move, coupled with uncertainty over how NIH would react. Based on conversations with officials of the NIH Office of Technology Transfer, NIH was known to believe it had a case against a march-in, asserting that publication was a way to "otherwise promote" commercialization under terms of the FTTA of 1986. Given that the initial publication decision, however, was made by Venter and submitted by him to *Science* even before Reid Adler knew about it would be an awkward position for NIH to defend, as ITS effort for commercialization (as opposed to the inventor's). Of course the matter will not be tested, and perhaps that is just as well. After all, the total number of EST sequences in question here amounts to only about a week of TIGR's output, a fact that may have come into play in making the decision not to pursue patent rights.

In his September 1992 testimony, Venter was quite explicit in opposing Senator Mark Hatfield's proposed moratorium on gene patenting. Venter predicted that "at the rate of gene discovery now possible, virtually all human genes will have been sequenced by the time the moratorium proposed by Senator Hatfield would end. If, due to this moratorium, the sequence

data are not published, medical research will be delayed immeasurably" (p. 59)[78]. Venter argued that patenting was the best means to promote public access to sequence data, noting that "my laboratory has published more human genome sequence data, including both chromosomal sequences and EST sequences, than any other laboratory in the US or abroad" (p. 60)[78]. Venter argued that the alternative to patenting was trade secrecy, if commercial applications were to be pursued. This would clearly apply to commercial firms and university or other groups with industrial research agreements (including universities and private research centers), but obviously lots of sequences would be published, looping back to the open question about what that will do to patentability of full-length genes (for partial sequences) and functional characterization (when patent granted without known or for a different biological function).

Dr. Venter also argued that absent cDNA patent protection, US firms but not foreign ones would be prevented from finding sufficient protection to warrant substantial private investment. The rationale was not spelled out, but was presumably premised on some foreign countries' granting patent rights that could induce their domestic biotechnology and pharmaceutical industries to invest in genome research, while US failure to protect any DNA patents would undermine US investments in any otherwise patentable DNA-based biotechnology research. Given the recent history of peptide pharmaceuticals, this view is quite plausible, although whether it extends sufficiently to cover EST patents (as opposed to, for example, EPO or TPA) is open to question.

Venter went on to suggest that the EST patent issue might disappear if the patent law were clarified to eliminate the possibility that publication of a partial gene sequence would preclude subsequent patenting of a more fully characterized gene, with the following language: "Prior art shall not preclude patentability of an amino acid or a nucleotide sequence solely because such prior art discloses a portion of such sequence" (p. 64)[78].

A final note of interest is Venter's statement in a letter to Senator DeConcini subsequent to his testimony, where he noted that "there has been insufficient attention paid to the moral and

ethical issues that arise from gene or animal patenting. I am strongly against patenting human cells, tissues, organs or any animal... Genetic reductionists argue that genes are life forms or equivalent to life. I strongly believe that we are much more than the sum total of our genetic composition" (p. 67)[77].

In a letter to the author, Bruce Cameron of TIGR notes that TIGR's public position on patenting has evolved since Dr. Venter's testimony. As a "not for profit research institution, TIGR considers decisions on patenting human gene inventions to be business decisions and does not participate in them. TIGR scientists, as the discoverers of human gene information, are contractually obligated to participate in HGSI patent applications, as appropriate, when called upon by HGSI to do so. TIGR is otherwise not involved in patent applications"[9].

That letter also confirms what has been publicly announced by Dr. Harold Varmus, in support of his decision to abandon the NIH EST patent applications, that Dr. Venter agreed not to assert inventor's rights to them before Varmus made his final decision [9].

Sagami Chemical Research Center

Address: 4-4-1 Nishi-Ohnuma
Sagamihara
Kanagawa 229
Japan

Phone: 81-427-42-4791
81-427-49-7631 fax

Founded: August 1963

Chairman of Board: Teruo Yawata; Kiyoshi Kondo Vice-Chair

Managing Director: Hideaki Makino

Other Directors: Kannosuke Nakamura (President, Kyowa Hakko Kogyo), Hisao Nakamura (Chair, Kuraray), Isao Masamune (Industrial Bank of Japan), Kazusuke Imamura (President, Onoda Cement), Akiyoshi Wada (formerly of Tokyo Univ.), Teiji Tsuruta (formerly of Tokyo Univ.), Takashi Sugimura (Past Pres, Nat. Cancer Center), and Madoka Tashiro (President, Tosoh).

Director of cDNA project (which is part of a larger project on human protein biophysics and biochemistry): Seishi Kato.

Funding: Funded privately, roughly half derived from corporate sponsors interested in chemical research (including Hitachi, Nissan, Tokyo Electric Power Co and Nippon Steel), and half from patent royalties. Most of these patents come from organic chemicals. The cDNA project, described below, was funded in part by the Kanagawa Prefecture, the regional government.

Research Plan — description of the cDNA project: The first phase of the cDNA project began in April 1991 and is planned through March 1994. There are six researchers, with 2 ABI sequenators and two Seiko biochemical robots. The process begins with synthesis of full-length

cDNAs from mRNAs, followed by cloning, sequencing, and characterization of the product. A patent on 60 full length cDNAs was filed in the US and Japan. The patent application was based on sequence information and inferred function, not isolated full-length genes or purified gene products. The patent application is not public, and became publicly known through the visit of a reporter from the Japanese business paper, *Nikkei Shimbun*. It was then picked up by US papers and *Nature* [70].

In a letter to me, Seishi Kato explained that "I started random sequencing of human cDNAs in 1985 and found that this strategy is an effective way to discover novel proteins... I have developed new vectors and techniques for synthesizing a full-length cDNA library and characterizing the cDNA clones... Our present purpose is to collect the sequence-determined cDNA clones from which the encoded proteins can be produced... and to distribute them to researchers in life science as seeds. Our cDNA collection is available for all researchers who are interested in the particular cDNA clone"[45]...

Comments on DNA patenting and technology transfer: Kato's letter also explains the Sagami Chemical Research Center's current policy, "we should apply for a patent if we have gotten patentable results, because half of the income of our institute comes from a patent fee"[45].

Other cDNA patenting efforts in Japan. While other private research institutes and firms in Japan are now known to have filed cDNA patent applications based on partial sequence data, it is known that Ohtsuka Pharmaceuticals intends to use a cDNA sequencing approach to intractable neurological disorders, in hopes of finding diagnostics and therapeutics. A research team affiliated with Yusuke Nakamura of the Cancer Institute of Japan has been pursuing genome research in collaboration with Ohtsuka, focusing 15 members of his research team on genomics, and using 8 sequencing machines[54]. The team has isolated cDNAs from fetal brain and is now pursuing full-length cDNA sequences. Ohtsuka has not yet filed patent applications, but has stated that it expects to do so [55]. In addition to the many other Japanese pharmaceutical companies that may be pursuing similar lines of research but who have not discussed their

strategies publicly (with Mitsuru Miyata of Nikkei Biotech, the editor who first published the Sagami and Ohtsuka stories), Chiba prefecture and some private firms (including Fujitsu, Canon, Nissan Chemical, Denki Kagaku Kogyo, Nippon Zeon, Maruzen Petrochemical, and Tokyo Tanabe) have begun construction of the Kazusa Academic Park, which is expected to house a major DNA sequencing facility on its 1000 hectare campus. The Institute has been allocated ¥15 billion ($136 million), and is expected to open this fall[59]. It currently houses 18 DNA sequencers, and a staff expected to grow considerably over the next few years.

A few parting comments (not to be shared outside OTA)

The companies divide into two general categories, although some cross the boundaries. Most companies intend to follow positional cloning strategies to find genes, isolate them, and patent the resulting gene with an eye to diagnostics and possible therapeutic usefulness. The therapeutics can derive from regulation, gene therapy, antisense, or providing a target (or in some cases a lead compound) for drug development. The positional cloning companies include Collaborative Research, Mercator, Millennium, Myriad, and Sequana. Collaborative Research, Incyte, and Human Genome Sciences/TIGR premise a substantial part of their gene discovery process on high speed DNA sequencing. Collaborative is sequencing mycobacterial genomes, and has applied to perform genomic sequencing (not cDNAs) from chromosomes 10 and 20. Incyte and Human Genome Sciences are racing after mainly human genes, starting from cDNAs, taken from different tissues and functional states. Darwin proposes to start with a genomic front end, emphasizing sequencing, and then proceed to discovery of new lead compounds by molecular evolution. All of the companies will have to rely on clinical classification and evaluation, genetic linkage, physical mapping, DNA sequencing, and informatics, but the relative emphasis varies among them.

It is quite difficult to precisely state how much the companies are worth in aggregate. The table at the end of this note portrays what I have been able to glean about the financial status of the various firms. Collaborative Research is really a first generation biotechnology company that this year transformed itself into a genome research company similar in its technology to the others, but not in its philosophy of pursuing federal grants and contracts as a central element of corporate development. Its operating capital of $5.3 million at the end of fiscal year 1993 compares to Mercator's startup status, Millennium's $8.5 million, Myriad's $11.3 million, and Sequana's more than $12 million in capital. Incyte started as a contract research startup working on bacterial proteins, but shifted last year to the cDNA sequencing strategy and raised $17.45 million late in 1993, based mainly on investors' faith that its sequencing approach might work.

HGSI obtained $59 million from SmithKline Beecham and added a couple million publicly traded stock worth another $40 million or so at the end of 1993. HGSI also stood to secure another $50 million plus substantial cash from another SmithKline Beecham stock purchase if it met its first two of milestones, as it was expected to do early in 1994. Its stock value and commitments of up to $125 million from SmithKline Beecham must be offset by its commitment to give TIGR up to $85 million over ten years, although this contribution from HGSI could be shifted substantially to Plant Genome and Industrial Genome Sciences if they become fully capitalized. Darwin's finances are not at all clear, except that it has found difficulties in reaching its hoped-for $50 million initial investment.

The companies appear to have garnered or retained operating capital of something on the order of $160 million. This assumes $5.3 million operating capital at CRI, $99 million for HGSI [from $40 million stock and $59 payments already received from SKB], $17.45 million for Incyte stock, $8.5 million Millennium startup funding, $8.8 million funding for Myriad (the publicly disclosed $11.3 million less 2/3 of the $1.8 million 3-year agreement with Lilly, on the assumption that these payments have not been made), and Sequana's more than $12 million. These add to $151 million. Mercator and Darwin are conspicuously silent about their financial status, but they are at least partially capitalized, probably enough to go near or over the $160 million mark. This leaves out companies doing genome-related research of a different sort, such as contract sequencing companies, and DNA sequencing instrument/process companies (Genomyx, SeQ, others).

The vast bulk of the funding for the companies surveyed came in calendar year 1993 (all of HGSI's value, all of Darwin's, Incyte's stock, most of Myriad's new investment, all of Millennium's investment, and most of Sequana's and Mercator's startup funding). In an otherwise bleak year for biotechnology startups, this is a truly remarkable phenomenon. It suggests the minimum magnitude of investment being made on the presumption that something patentable will come out of genome research.

Of the public documents, the prospectus from Human Genome Sciences, Inc., is most specific about the research strategy, intellectual property protection, and commitment to protect trade secrets. The documents filed with SEC provide an even more detailed look at an extremely complex business arrangement between TIGR (a private nonprofit research institute), HGSI (a for-profit genome research company focusing on sequencing and informatics), and SKB (a fully integrated transnational pharmaceutical house tilting its entire research effort toward genome research). The materials from other firms are generally more vague and difficult to evaluate, although CRI's general approach is quite straightforward in its reliance on federal grants and contracts. The positional cloning companies are clear in their aspirations, but the business plans are generally far sketchier, and none is publicly traded.

Human Genome Sciences is also by far the most substantially capitalized among the lot, the largest (in number of employees, informatic resources, equipment and aggregate laboratory space, especially if TIGR is taken into account), and appears poised to pull ahead of Incyte in sequencing throughput in the near future, by dint of its larger capacity for sequencing and informatics.

The Sagami Chemical Research Center is a small player in this drama by technical measures, but likely to loom large as a political presence. The MRC's cDNA effort, whose patents have now been abandoned, and CEPH/Genethon's cDNA efforts make the picture murky, as their substantial cDNA sequences will surely overlap with HGSI, Incyte, Ohtsuka, Sagami, and other efforts linked to patent applications. The abandonment of the NIH patent applications does not eliminate the issues, it mainly drives them underground for awhile. The Sagami Center's application may well be of far more rhetorical than industrial significance. The reports on Sagami and Ohtsuka will surely be noted in any congressional debate about the prudence of constraining DNA patents. The modest Japanese research efforts seem destined to attain much greater potency in the realm of political rhetoric.

Every company surveyed will rely heavily on patent protection of genes uncovered through company research. They differ in the kind of protection that would be most beneficial, and might well differ in their opinion of whether patents should be issued on ESTs, but agreement on the patentability of DNA in general is a bedrock principle for all these firms. They differ markedly in their approach to technology transfer from federally funded research. HGSI went so far as to buy out a DOE grant application from TIGR, as it did not want the intellectual property rights encumbered with federal pricing clauses or other possible sources of "contamination." Part of the drive here may have been a need to be squeaky clean amidst what must have been a delicate negotiation with SKB at the time, but it is nonetheless a concrete example that there is real fear of "government contamination"-- at least a million dollars' worth. At the other extreme, Collaborative Research is vigorously pursuing research grants, SBIR grants, and federal contracts as a centerpiece in its corporate strategy. It is thus critically dependent on clean transfer of patent and other rights from federally funded research. To my knowledge, none of the firms is attached to NIH, DOE or other GOGO or GOCO laboratories through CRADAs. The potential impact of the DHHS pricing clause on federal collaboration thus cannot be assessed directly. Whether they would have pursued CRADAs without the AZT controversy and the pricing clause simply cannot be ascertained.

References

These are references cited in the text. The separate bibliography includes these, and also other articles (many contributed by the companies) that were not cited.

1. Anonymous (1993). American Stock Exchange Prices. *Washington Post* (29 December): D8.

2. Anonymous (1993). Millennium's Genetic Maps of Disease. *Bernstein Report on Business* (9 August): B1.

3. Anonymous (1993). NASDAQ National Market Prices. *Washington Post* (29 December): D8.

4. Anonymous (1993). Sequana Therapeutics, Inc. *In Vivo: The Business & Medicine Report* **11** (No. 12, February): 17, 19.

5. Anonymous (1993). Top Scientists Form Company. *Biotechnology Business News, Financial Times* **3** (13 August).

6. Beaudry, Amber A. and Gerald F. Joyce (1992). Directed Evolution of an RNA Enzyme. *Science* **257** (31 July): 635-641.

7. Botstein, David, Raymond L. White, Mark Skolnick and Ronald W. Davis (1980). Construction of a Genetic Linkage Map in Man Using Restriction Fragment Length Polymorphisms. *American Journal of Human Genetics* **32** : 314-331.

8. Bovsun, Mara (1993). Sequana Probing Fat-Mouse Genome for DNA Diet Tips. *McGraw-Hill Biotechnology Newswatch* (19 July): 1, 3, 4.

9. Cameron, Bruce. (1994). Letter to Robert Cook-Deegan, OTA contractor. 23 February. The Institute for Genomic Research.

10. Collaborative Research, Inc. (1993). 1993 Annual Report. 29 November. Collaborative Research, Inc.

11. Collaborative Research, Inc. (1993). Background Paper: Genome Research: Application to Infectious Disease. 31 December. Collaborative Research, Inc.

12. Collaborative Research, Inc. (1993). Form 10-K: Annual Report to Securities and Exchange Commission for fiscal year ending 31 August 1993 (SEC file # 0-10824). 22 November. Collaborative Research, Inc.

13. Collaborative Research, Inc. (1994). Background Paper: Genome Research. 31 January. Collaborative Research, Inc.

14. Collaborative Research, Inc. (1994). Background paper: Turning Genetic Information into Therapeutic Products. 31 January. Collaborative Research, Inc.

15. Donis-Keller, Helen, Philip Green, C. Helms and et al. (1987). A Genetic Linkage Map of the Human Genome. *Cell* **51** (October): 319-337.

16. Eloi, Fenel M. (1993). Press release: Collaborative Research Reports Improved First Quarter Results. 20 December. Collaborative Research, Inc.

17. Feng, Qing, Tae Kyo Park and Julius Rebek (1992). Crossover Reactions between Synthetic Replicators Yield Active and Inactive Recombinants. *Science* **256** (22 May): 1179-1180.

18. Friedman, Orrie M. (1993). First Quarterly Report to stockholders. 16 February. Collaborative Research, Inc.

19. Friedman, Orrie M. and Robert J. Hennessey. (1993). Second Quarter Report to stockholders. 5 May. Collaborative Research, Inc.

20. Gambon, Jill (1993). Millennium Deal Gets $8.5 Million in Seed Capital. *Boston Business Journal* **13** (13 August).

21. Hall, Stephen S. (1987). Invisible Frontiers: The Race to Synthesize a Human Gene. New York, Atlantic Monthly Press; paperback Tempus Press.

22. Hennessey, Robert J. (1993). Third quarter report to stockholders. 23 August. Collaborative Research, Inc.

23. Hennessey, Robert J., Gerald F. Vovis and John P. Richard. (1994). Interview at CRI, 100 Beaver Street, Waltham Massachusetts. 25 February. Collaborative Research, Inc.

24. Horwitz, Marshall S. Z., Dipak K. Dube and Lawrence A. Loeb (1989). Selection of New Biological Activities from Random Nucleotide Sequences: Evolutionary and Practical Considerations. *Genome* **31** : 112-117.

25. Human Genome Sciences, Inc. (1992). Background documents submitted to SEC for initial public offering: Research Services Agreement (between Human Genome Sciences, Inc.,

and The Institute for Genomic Research), pp. 293-337, exhibit 10.6. 1 October. Human Genome Sciences, Inc.

26. Human Genome Sciences, Inc. (1992). Documents submitted to SEC for intial public offering: Consulting Agreement (between HGSI and William Haseltine), pp. 461-470, exhibit 10.14. 1 November. Human Genome Sciences, Inc.

27. Human Genome Sciences, Inc. (1992). Documents submitted to SEC for intial public offering: Intellectual Property Agreement (between HGSI and TIGR), pp. 609-636, exhibit 10.5, pp. 317-337. 2 October. Human Genome Sciences, Inc.

28. Human Genome Sciences, Inc. (1993). Background documents filed with Securities and Exchange Commission for Initial Public Offering in December 1993: Intellectual Property Agreement (between Human Genome Sciences, Inc., and Plant Genome Sciences, Inc.), pp. 90-114. 17 November. Human Genome Sciences, Inc.

29. Human Genome Sciences, Inc. (1993). Background Documents to SEC for Initial Public Offering in December, 1993: Collaboration Agreement (between Human Genome Sciences, Inc., and SmithKline Beecham Corp.). 19 May. Human Genome Sciences, Inc.

30. Human Genome Sciences, Inc. (1993). Documents submitted to SEC for intial public offering: Employment Agreement (between HGSI and William Haseltine), pp. 485-503, exhibit 10.16. 7 May. Human Genome Sciences, Inc.

31. Human Genome Sciences, Inc. (1993). Documents submitted to SEC for intial public offering: Intellectual Property Agreement (between HGSI and Industrial Genome Sciences, Inc.), pp. 894-910, exhibit 10.41. 18 March. Human Genome Sciences, Inc.

32. Human Genome Sciences, Inc. (1993). Documents submitted to SEC for intial public offering: Letter from J. Craig Venter to Wallace Steinberg, representing an agreement between HGSI and TIGR for cDNA sequencing, pp. 355-358, exhibit 10.8. 19 April. Human Genome Sciences, Inc.

33. Human Genome Sciences, Inc. (1993). Documents submitted to SEC for intial public offering: Letter from J. Craig Venter, The Institute for Genomic Research, to Lewis J. Shuster, Executive Vice President, Human Genome Sciences, Inc. regarding withdrawal of a Department of Energy Grant in return for HGSI funding, pp. 351-353, exhibit 10.x. 31 March. Human Genome Sciences, Inc.

34. Human Genome Sciences, Inc. (1993). Prospectus: 2,250,000 shares common stock. 1 December. Lehman Brothers; Bear, Stearns & Co., Inc.; Smith Barney Shearson, Inc.

35. Hurst, Laurence D. and Richard Dawkins (1992). Life in a Test Tube. *Nature* ? (21 May).

36. Incyte Pharmaceuticals, Inc. (1992). Press release: Incyte and Ciba-Geigy Resolve Patent Interference on Protease Nexin-1. 29 September. Incyte Pharmaceuticals, Inc.

37. Incyte Pharmaceuticals, Inc. (1993). Exhibit 10.10: Patent Assignment Agreement (between Incyte and Ciba-Geigy). filed as background for initial public offering, November 1993, pp. 325-340. Incyte Pharmaceuticals, Inc.

38. Incyte Pharmaceuticals, Inc. (1993). Press release: Incyte and Genentech Revise Co-Development Agreement for BPI. 18 March. Incyte Pharmaceuticals, Inc.

39. Incyte Pharmaceuticals, Inc. (1993). Press release: Incyte closes IPO; Underwriter Exercises Over-Allotment. 12 November. Incyte Pharmaceuticals, Inc.

40. Incyte Pharmaceuticals, Inc. (1993). Press release: Incyte Pharmaceuticals and the Mayo Clinic Extend Discovery Program on Inflammation and Allergy. 2 March. Incyte Pharmaceuticals, Inc.

41. Incyte Pharmaceuticals, Inc. (1993). Prospectus: 2,000,000 shares common stock. 4 November. D. Blech & Co., Inc.

42. Incyte Pharmaceuticals, Inc. (1994). Background paper: Biology "In Silico" — Biology Moves from the Bench to the Chip: Incyte Uses High-Throughput Sequencing for Drug Discovery. Incyte Pharmaceuticals, Inc.

43. Isonaka, Diane. (1994). Fax and e-mail note to Robert Cook-Deegan, OTA contractor: "Darwin's Statement on Intellectual Property Rights". 21 February. Darwin Molecular Corp.

44. Joyce, Gerald F. (1992). Directed Molecular Evolution. *Scientific American* (December): 90-97.

45. Kato, Seishi. (1993). Letter to Robert Cook-Deegan. 24 December. Sagami Chemical Research Center.

46. Kinsella, Kevin. (1993). Phone interview. 31 December. Sequana Therapeutics, Inc.

47. Kinsella, Kevin. (1994). Corrections and comments on marked copy of draft OTA contract report. 18 February. Sequana Therapeutics, Inc.

48. Lander, Eric S. and David Botstein (1987). Homozygosity Mapping: A Way to Map Recessive Traits in Humans by Studying the DNA of Inbred Children. *Science* **236** : 1567-1570.

49. Maxam, Allan M. and Walter Gilbert (1977). A New Method for Sequencing DNA. *Proceedings of the National Academy of Sciences (USA)* **74** (February): 560-564.

50. Mercator Genetics, Inc. (1993). Public information packet. 16 December. Mercator Genetics, Inc., sent by Jeanne Gutfield, Administrative Assistant for Dennis Drayna.

51. Michelinie, Susan E. (1994). Press release: Collaborative Research Applauds NIH Decision to Drop DNA Gene Fragment Patent Applications. 17 February. Collaborative Research, Inc.

52. Millennium Pharmaceuticals, Inc. (1993). Fact Sheet. Fall. Millennium Pharmaceuticals, Inc.

53. Millennium Pharmaceuticals, Inc. (1993). Press release: Top Genome Scientists Form Biotechnology Company to Identify Disease-Causing Genes for Therapeutic Development. 4 August. Millennium Pharmaceuticals, Inc.

54. Miyata, Mitsuru (1994). Ohtsuka Pharmaceutical Company to Develop Diagnostic Medicine, Therapeutic Medicine, and Food Based on DNA Analysis. *Nikkei Biotechnology* (17 Janaury): kindly translated by Foreign Broadcast Information Service.

55. Miyata, Mitsuru. (1994). Phone interview. 2 February. Nikkei Biotechnology.

56. Myriad Genetics, Inc. (1993). Executive Summary. 1 March. Myriad Genetics, Inc.

57. Myriad Genetics, Inc. (1993). Fact Sheet. Myriad Genetics, Inc.

58. Nelson, Stanley F., John H. McCusker, Mark A. Sander, Yun Kee, Paul Modrich and Patrick O. Brown (1993). Genomic Mismatch Scanning: A New Approach to Genetic Linkage Mapping. *Nature Genetics* **4** (May): 11-18.

59. Nikkan Kogyo Shimbun (1994). Kazusa DNA Research Institute at the Kazusa Academia Park. *Nikkan Kogyo Shimbun* (19 January): kindly translated by the Foreign Broadcast Information Service.

60. Park, Tae Kwo, Qing Feng and Julius Rebek (1992). Synthetic Replicators and Extrabiotic Chemistry. *Journal of the American Chemical Society* **114** (No. 12): 4529-4532.

61. Peterson, Lisa. (1994). Letter to Robert Cook-Deegan, OTA contractor, along with copy of draft contract report marked up by Randal Scott and Roy Whitfield of Incyte. 24 February. Incyte Pharmaceuticals, Inc.

62. Reynolds, Sherry L. (1994). Letter to Robert Cook-Deegan, OTA contractor, and copy of draft marked by Millennium corporate officers. 22 February. Millennium Pharmaceuticals, Inc.

63. Richard, John P. (1993). Press release: Collaborative Research, Inc., and Harvard Medical School Sign Exclusive License for Multiplex Seqeuncing. 29 November. Collaborative Research, Inc.

64. Sandburg, Brenda (1993). Sequana Partnership to Map Osteo Genes. *BioWorld Today* **4** (No. 169, 31 August): 1.

65. Sandburg, Brenda (1993). Sequana, Alopex Team Up to Map Baldness Genes. *BioWorld Today* **4** (177, 13 September): 1.

66. Schultz, Tammy. (1994). Letter to Robert Cook-Deegan, OTA contractor, along with draft contract report marked up by Peter Meldrum, President of Myriad Genetics, Inc. 16 February. Myriad Genetics, Inc.

67. Sequana Therapeutics. (1993). Press release: Sequana Therapeutics and Jackson Laboratory Announce Collaboration to Study Genetic Causes of Obesity. 29 June. Sequana Therapeutics, Inc.

68. Sequana Therapeutics, Inc. (1993). News release: Sequana and Alopex to Map Genes for Common Disorders. 13 September. Sequana Therapeutics, Inc.

69. Sequana Therapeutics, Inc. (1993). News release: Sequana Therapeutics and Southwest Foundation to Map Genes Associated with Osteoporosis. 30 August. Sequana Therapeutics, Inc.

70. Swinbanks, David (1993). Institute Files for Patents on First Japanese Sequences. *Nature* **361** (18 February): 576.

71. Technical Insights, Inc. (1993). Company to Watch. *Genetic Technology News, Section of Biotechnology Information Package* **13** (November).

72. The Institute for Genomic Research. (1994). Information brochure. The Institute for Genomic Research.

73. Tsui, Lap-Chee, Manuel Buchwald, et al. (1985). Cystic Fibrosis Locus Defined by a Genetically Linked Polymorphic DNA Marker. *Science* **230** (29 November): 1054-1057.

74. van Brunt, Jennifer (1993). Incyte Gets Third Patent for BPI. *BioWorld Today* **4** (26 August): 1.

75. van Brunt, Jennifer (1993). New Company Sequana Studies Obesity in Mice. *BioWorld Today* **4** (No. 125, 29 June): 1.

76. van Brunt, Jennifer (1993). Scientists Embark on New Millennium. *BioWorld Today* **4** (4 August): 1.

77. Venter, J. Craig. (1992). Letter to Senator Dennis DeConcini. 1 December. From The Institute for Genomic Research to the Committee on the Judiciary, US Senate.

78. Venter, J. Craig. (1992). Statement of J. Craig Venter, Ph.D., President and Director, The Institute for Genomic Research, Before the Subcommittee on Patents, Copyrights, and Trademarks, Senate Judiciary Committee. 22 September. Serial No. J-102-83. Committee on the Judiciary, US Senate.

79. Vovis, Gerald F. (1993). Press release: Collaborative Research Awarded Genomic Research Grants and Contracts Totalling $2,000,000. 16 December. Collaborative Research, Inc.

80. Vovis, Gerald F. (1994). List of federal grants and contracts. 28 February. Collaborative Research, Inc.

COLLABORATIVE RESEARCH, INC
CURRENTLY ACTIVE GRANTS AND CONTRACTS

1) National Center for Human Genome Research
05/01/91 through 04/30/94
"Physical & Refined Genetic Map of Human Chromosome 10"
Construct a complete physical map of human chromosome 10.
R01 Grant: $1,686,843

2) National Center for Human Genome Research
08/01/91 through 07/31/94
"High Throughput Multiplex Sequencing"
Reduce computer-assisted multiplex sequencing to practice while sequencing the genomes of **Mycobacterium tuberculosis** and **M. leprae.**
R01 Grant: $5,494,162

3) Muscular Dystrophy Association
02/01/92 through 01/31/95
"Cloning the Gene for Facioscapulohumeral MD"
Clone the gene on 4q responsible for causing Facioscapulohumeral Muscular Dystrophy.
Grant: $464,272

4) National Institute of General Medical Sciences
02/01/92 through 01/31/95
"PCR-Based DNA Typing System"
Develop population databases for highly polymorphic Variable Numbers of Tandem Repeat (VNTR) and microsatellite repeat loci using PCR.
Phase II SBIR Grant: $500,000

5) Department of Energy
03/15/92 through 03/14/95
"Chimera-Free, High Copy Number YAC Libraries and Efficient Methods of Analysis"
Create a five-genome equivalent Yeast Artificial Chromosome (YAC) library suitable for subcloning and sequencing.
Grant: $922,000

6) National Cancer Institute
09/01/92 through 08/31/94
"A DNA Probe Test for Debrisoquine Hydroxylase Phenotype"
Identify the remaining 5% of CYP2D6 alleles and design PCR-based tests and determine population frequencies for these alleles.
Phase II SBIR Contract: $499,987

7) Department of Veterans Affairs
09/08/92 through 09/07/94
"A Genetic Linkage Study of Schizophrenia"
Goal of the present portion of the project is to establish lymphoblast cell lines for 320 individuals from families with one affected parent and at least two affected offspring.
Contract: $63,068

COLLABORATIVE RESEARCH, INC
CURRENTLY ACTIVE GRANTS AND CONTRACTS (con't)

8) National Institute of Mental Health
09/30/92 through 03/31/95
"Genotyping"
Determine the genetic location of the gene(s) responsible for bipolar affective disorder.
Contract: $1,079,360

9) National Institute of General Medical Sciences
01/01/93 through 12/31/94
"Allele-Specific Multiplex DNA Diagnostic Test"
Develop a new, faster, and more convenient DNA diagnostic test which can simultaneously detect many mutant alleles at many different genetic loci.
Phase II SBIR Grant: $500,000

10) National Institute of Environmental Health Sciences
04/01/93 through 03/31/94 with four one year options
"DNA Sequence Analysis"
Determine the DNA sequence of M13 mutant clones.
Contract: $128,180 for the first year

11) National Center for Human Genome Research
04/01/93 through 03/31/95
"PCR Development and Localization of CRI RFLP Probes"
Using index markers, i. e. PCR-based genetic markers with heterozygosities ≥ 0.7, complete the development of framework maps for human chromosomes 10 and 20.
Phase II SBIR Grant: $500,000

12) National Center for Human Genome Research
07/01/93 through 03/31/94
"Comprehensive Sequence Assembly Algorithm"
Develop a general purpose sequence assembly algorithm and corresponding software.
Phase I SBIR Grant: $50,000

13) National Institute of Mental Health
09/01/93 through 04/05/94
"A Set of Mapping Panels for Localizing Human Genetic Diseases"
Develop a set of genetic maps for all human autosomes and the X chromosome that incorporate markers which are sufficiently polymorphic and spaced at appropriate intervals to make them useful for disease gene mapping.
Phase I SBIR Contract: $50,000

COLLABORATIVE RESEARCH, INC
CURRENTLY ACTIVE GRANTS AND CONTRACTS (con't)

14) Department of Energy
09/08/93 through 04/01/94
"Non-Radioactive Detection Systems Based on Enzyme Fragment Complementation"
Develop an extremely sensitive, non-radioactive, binary detection system which will significantly increase the speed and reduce the cost of large-scale genome sequencing.
Phase I SBIR Grant: $75,000

15) National Institute of Neurological Disorders and Stroke
12/01/93 through 11/30/96
"Large Scale Automated DNA Sequencing of Human Genes Involved in Neurological Disorders"
Provide broad-based support to the NINDS intramural staff in genetic mapping, cloning, and sequencing of neurological disease genes.
Contract: $1,508,437

16) National Center for Human Genome Research
12/20/93 through 11/30/95
"Computer-Assisted Non-Radioactive Multiplex Genotyping"
Develop the technology which will allow high throughput, multiplex genotyping.
Phase II SBIR Grant: $500,000

Bibliography

This includes items not cited in the text, but which may nonetheless be of some use.
Some references are incomplete.

1. Alexander, Karen (1992). Biotech Stars Launching Firm. *Seattle Times* (20 November): D9.

2. Anderson, Christopher (1992). New French Genome Centre Aims to Prove that Bigger Really Is Better. *Nature* **357** (18 June): 526-527.

3. Anderson, Christopher (1992). US Genome Project Does It the French Way, Conceding that Size Matters After All. *Nature* **360** (3 December): 401.

4. Anderson, Christopher (1993). Genome Project Goes Commercial. *Science* **259** (15 January): 300-302.

5. Angier, Natalie (1993). Map of All Chromosomes to Guide Genetic Hunters. *New York Times* (16 December): A1, B14.

6. Anonymous (1993). American Stock Exchange Prices. *Washington Post* (29 December): D8.

7. Anonymous (1993). Millennium's Genetic Maps of Disease. *Bernstein Report on Business* (9 August): B1.

8. Anonymous (1993). NASDAQ National Market Prices. *Washington Post* (29 December): D8.

9. Anonymous (1993). Sequana Therapeutics, Inc. *In Vivo: The Business & Medicine Report* **11** (No. 12, February): 17, 19.

10. Anonymous (1993). Top Scientists Form Company. *Biotechnology Business News, Financial Times* **3** (13 August):

11. Associated Press (1993). Scientists Draw Human DNA Map. *Boston Globe* (16 December): ?

12. Beaudry, Amber A. and Gerald F. Joyce (1992). Directed Evolution of an RNA Enzyme. *Science* **257** (31 July): 635-641.

13. Bishop, Jerry E. (1993). New Way to Develop High-Tech Drugs Monkeys with Darwin's Famed Theory. *Wall Street Journal* (25 February): B1, B2?

14. Bluestone, Mimi (1992). Commercializing Genome Research. *Bio/Technology* **10** (May): 478-479.

15. Botstein, David, Raymond L. White, Mark Skolnick and Ronald W. Davis (1980). Construction of a Genetic Linkage Map in Man Using Restriction Fragment Length Polymorphisms. *American Journal of Human Genetics* **32** : 314-331.

16. Bovsun, Mara (1993). Sequana Probing Fat-Mouse Genome for DNA Diet Tips. *McGraw-Hill Biotechnology Newswatch* (19 July): 1, 3, 4.

17. Burris, Bill (1993). Studies into Fat Mice Have Human Obesity in Mind. *San Diego Daily Transcript* **108** (No. 87, 30 July):

18. Cameron, Bruce. (1994). Letter to Robert Cook-Deegan, OTA contractor. 23 February. The Institute for Genomic Research.

19. Carey, John (1992). This Genetic Map Will Lead to a Pot of Gold. *Business Week* (2 March): 74.

20. Carey, John and Joan O'C. Hamilton (1993). Gene Hunters Go for the Big Score. *Business Week* (16 August): 98-99.

21. Carey, John, Joan O'C. Hamilton, Laura Jereski and Emily T. Smith (1990). The Genetic Age. *Business Week* (28 May): 68-71, 74, 78, 82-83.

22. Cohen-Solal, Michel. (1993). Statement for OTA international workshop. ? Groupement d'Etudes et de Recherches sur les Genomes, Gif-sur-Yvette, France.

23. Collaborative Research, Inc. (1986). Genetic Engineering: The Future is Now. 1986 Annual Report (25th Anniversary Issue). Collaborative Research, Inc.

24. Collaborative Research, Inc. (1993). 1993 Annual Report. 29 November. Collaborative Research, Inc.

25. Collaborative Research, Inc. (1993). Background Paper: Genome Research: Application to Infectious Disease. 31 December. Collaborative Research, Inc.

26. Collaborative Research, Inc. (1993). Form 10-K: Annual Report to Securities and Exchange Commission for fiscal year ending 31 August 1993 (SEC file # 0-10824). 22 November. Collaborative Research, Inc.

27. Collaborative Research, Inc. (1994). Background Paper: Genome Research. 31 January. Collaborative Research, Inc.

28. Collaborative Research, Inc. (1994). Background paper: Turning Genetic Information into Therapeutic Products. 31 January. Collaborative Research, Inc.

29. Collins, Francis S. and David Galas (1993). A New Five-Year Plan for the U.S. Human Genome Project. *Science* **262** (1 October): 43-46.

30. Culotta, Elizabeth (1992). Forcing the Evolution of an RNA Enzyme in the Test Tube. *Science* **257** (31 July): 613.

31. Dajer, Tony (1993). Genetics 1992: The Genome Finds Its Henry Ford. *Discover* (January): 86-87.

32. Donis-Keller, Helen, Philip Green, C. Helms and et al. (1987). A Genetic Linkage Map of the Human Genome. *Cell* **51** (October): 319-337.

33. Edgington, Stephen M. (1993). Shape Space: Is Biopharmaceutical Discovery Entering a New Evolutionary Stage? *Bio/Technology* **11** (March): 285-289.

34. Eloi, Fenel M. (1993). Form 10-Q: Quarterly report for quarter ending 29 May 1993. 9 July. Collaborative Research, Inc.

35. Eloi, Fenel M. (1993). Press release: Collaborative Research Reports Improved First Quarter Results. 20 December. Collaborative Research, Inc.

36. Erickson, Jim (1993). Darwin Molecular Adds Another Star. *Seattle Post-Intelligencer* (21 June): ?

37. Feng, Qing, Tae Kyo Park and Julius Rebek (1992). Crossover Reactions between Synthetic Replicators Yield Active and Inactive Recombinants. *Science* **256** (22 May): 1179-1180.

38. Fikes, Bradley J. (1993). The High-Risk Search Begins to Cash in on Genes of Humans. *San Diego Business Journal* **14** (No. 39, 27 September):

39. Fisher, Lawrence M. (1994). Profits and Ethics Clash in Research on Genetic Coding. *New York Times* (30 January): 1, 18.

40. Friedman, Orrie M. (1993). First Quarterly Report to stockholders. 16 February. Collaborative Research, Inc.

41. Friedman, Orrie M. and Robert J. Hennessey. (1993). Second Quarter Report to stockholders. 5 May. Collaborative Research, Inc.

42. Friend, Tim Clues to Human Development Float in Nature's Gene Pool. *USA Today* ? (?): ?

43. Gambon, Jill (1993). Millennium Deal Gets $8.5 Million in Seed Capital. *Boston Business Journal* **13** (13 August):

44. Garcia, Nancy (1993). Galas to Head R&D at Darwin Molecular. *BioWorld Today* **4** (21 June): 1-2.

45. Gibbs, W. Wayt (1993). Natural Selection: Investors aren't buying into Darwin Molecular's evolution. *Scientific American* (September): 151-152.

46. Gorman, Christine (1993). The Race to Map Our Genes. *Time* (8 February): 57.

47. Hall, Stephen S. (1987). Invisible Frontiers: The Race to Synthesize a Human Gene. New York, Atlantic Monthly Press; paperback Tempus Press.

48. Hamilton, Joan O'C. and Naomi Freundlich (1990). The Technology Behind the Breakthroughs. *Business Week* (28 May): 82-83.

49. Hamilton, Joan O'C., Emily T. Smith, Larry Armstrong, Geoffrey Smith and Joseph Weber (1992). Biotech: America's Dream Machine. *Business Week* (2 March): 66-69, 72-74.

50. Hennessey, Robert J. (1993). Third quarter report to stockholders. 23 August. Collaborative Research, Inc.

51. Hennessey, Robert J., Gerald F. Vovis and John P. Richard. (1994). Interview at CRI, 100 Beaver Street, Waltham Massachusetts. 25 February. Collaborative Research, Inc.

52. Horwitz, Marshall S. Z., Dipak K. Dube and Lawrence A. Loeb (1989). Selection of New Biological Activities from Random Nucleotide Sequences: Evolutionary and Practical Considerations. *Genome* **31** : 112-117.

53. Human Genome Sciences, Inc. (1992). Background documents submitted to SEC for initial public offering: Research Services Agreement (between Human Genome Sciences, Inc., and The Institute for Genomic Research), pp. 293-337, exhibit 10.6. 1 October. Human Genome Sciences, Inc.

54. Human Genome Sciences, Inc. (1992). Documents submitted to SEC for intial public offering: Consulting Agreement (between HGSI and William Haseltine), pp. 461-470, exhibit 10.14. 1 November. Human Genome Sciences, Inc.

55. Human Genome Sciences, Inc. (1992). Documents submitted to SEC for intial public offering: Intellectual Property Agreement (between HGSI and TIGR), pp. 609-636, exhibit 10.5, pp. 317-337. 2 October. Human Genome Sciences, Inc.

56. Human Genome Sciences, Inc. (1993). Background documents deposited at SEC for initial public offering of HGSI stock: Series B Convertible Preferred Stock Purchase Agreement, pp. 233-278. 19 May. Human Genome Sciences, Inc.

57. Human Genome Sciences, Inc. (1993). Background documents filed with Securities and Exchange Commission for Initial Public Offering in December 1993: Intellectual Property Agreement (between Human Genome Sciences, Inc., and Plant Genome Sciences, Inc.), pp. 90-114. 17 November. Human Genome Sciences, Inc.

58. Human Genome Sciences, Inc. (1993). Background Documents to SEC for Initial Public Offering in December, 1993: Collaboration Agreement (between Human Genome Sciences, Inc., and SmithKline Beecham Corp.). 19 May. Human Genome Sciences, Inc.

59. Human Genome Sciences, Inc. (1993). Documents submitted to SEC for intial public offering: Employment Agreement (between HGSI and William Haseltine), pp. 485-503, exhibit 10.16. 7 May. Human Genome Sciences, Inc.

60. Human Genome Sciences, Inc. (1993). Documents submitted to SEC for intial public offering: Intellectual Property Agreement (between HGSI and Industrial Genome Sciences, Inc.), pp. 894-910, exhibit 10.41. 18 March. Human Genome Sciences, Inc.

61. Human Genome Sciences, Inc. (1993). Documents submitted to SEC for intial public offering: Letter from J. Craig Venter to Wallace Steinberg, regarding use of TIGR sequencing equipment, p. 360, exhibit 10.9. 7 May. Human Genome Sciences, Inc.

62. Human Genome Sciences, Inc. (1993). Documents submitted to SEC for intial public offering: Letter from J. Craig Venter to Wallace Steinberg, representing an agreement between HGSI and TIGR for cDNA sequencing, pp. 355-358, exhibit 10.8. 19 April. Human Genome Sciences, Inc.

63. Human Genome Sciences, Inc. (1993). Documents submitted to SEC for intial public offering: Letter from J. Craig Venter, The Institute for Genomic Research, to Lewis J. Shuster, Executive Vice President, Human Genome Sciences, Inc. regarding withdrawal of a Department of Energy Grant in return for HGSI funding, pp. 351-353, exhibit 10.7. 31 March. Human Genome Sciences, Inc.

64. Human Genome Sciences, Inc. (1993). Documents submitted to SEC for intial public offering: Letter from J. Craig Venter, The Institute for Genomic Research, to Lewis J. Shuster, Executive Vice President, Human Genome Sciences, Inc. regarding withdrawal of

a Department of Energy Grant in return for HGSI funding, pp. 351-353, exhibit 10.x. 31 March. Human Genome Sciences, Inc.

65. Human Genome Sciences, Inc. (1993). Documents submitted to SEC for intial public offering: Letter from J. Craig Venter, The Institute for Genomic Research, to Lewis J. Shuster, Executive Vice President, Human Genome Sciences, Inc. regarding withdrawal of a Department of Energy Grant in return for HGSI funding, pp. 351-353, exhibit 10.x. 31 March. Human Genome Sciences, Inc.

66. Human Genome Sciences, Inc. (1993). Documents submitted to SEC for intial public offering: Restricted Stock Purchase Agreement (between HGSI and William Haseltine), pp. 609-636, exhibit 10.x. 18 May. Human Genome Sciences, Inc.

67. Human Genome Sciences, Inc. (1993). Prospectus: 2,250,000 shares common stock. 1 December. Lehman Brothers; Bear, Stearns & Co., Inc.; Smith Barney Shearson, Inc.

68. Hurst, Laurence D. and Richard Dawkins (1992). Life in a Test Tube. *Nature* ? (21 May): ?

69. Incyte Pharmaceuticals, Inc. (1992). Press release: Incyte and Ciba-Geigy Resolve Patent Interference on Protease Nexin-1. 29 September. Incyte Pharmaceuticals, Inc.

70. Incyte Pharmaceuticals, Inc. (1993). Appendix I: Sample Materials Transfer Agreements for Collaborations with Academic and Corporate Collaborators. Filed as background for initial public offering, November 1993, pp. 320-324. Incyte Pharmaceuticals, Inc.

71. Incyte Pharmaceuticals, Inc. (1993). Exhibit 10.10: Patent Assignment Agreement (between Incyte and Ciba-Geigy). filed as background for initial public offering, November 1993, pp. 325-340. Incyte Pharmaceuticals, Inc.

72. Incyte Pharmaceuticals, Inc. (1993). Press release: Incyte and Genentech Revise Co-Development Agreement for BPI. 18 March. Incyte Pharmaceuticals, Inc.

73. Incyte Pharmaceuticals, Inc. (1993). Press release: Incyte closes IPO; Underwriter Exercises Over-Allotment. 12 November. Incyte Pharmaceuticals, Inc.

74. Incyte Pharmaceuticals, Inc. (1993). Press release: Incyte Pharmaceuticals and the Mayo Clinic Extend Discovery Program on Inflammation and Allergy. 2 March. Incyte Pharmaceuticals, Inc.

75. Incyte Pharmaceuticals, Inc. (1993). Prospectus: 2,000,000 shares common stock. 4 November. D. Blech & Co., Inc.

76. Incyte Pharmaceuticals, Inc. (1994). Background paper: Biology "In Silico" — Biology Moves from the Bench to the Chip: Incyte Uses High-Throughput Sequencing for Drug Discovery. Incyte Pharmaceuticals, Inc.

77. Isonaka, Diane. (1994). Fax and e-mail note to Robert Cook-Deegan, OTA contractor: "Darwin's Statement on Intellectual Property Rights". 21 February. Darwin MOlecular Corp.

78. Joyce, Gerald F. (1992). Directed Molecular Evolution. *Scientific American* (December): 90-97.

79. Kato, Seishi. (1993). Letter to Robert Cook-Deegan. 24 December. Sagami Chemical Research Center.

80. Kaufman, Ron (1993). Former DOE Genome Project Director to Oversee Biotech Launch. *The Scientist* **7** (26 July): ?

81. Kinsella, Kevin. (1993). Phone interview. 31 December. Sequana Therapeutics, Inc.

82. Kinsella, Kevin. (1994). Corrections and comments on marked copy of draft OTA contract report. 18 February. Sequana Therapeutics, Inc.

83. Kolata, Gina (1992). Laying Pipe for the Fountain of Youth. *New York Times* (1 November): F7?

84. Lander, Eric S. (1993). Finding Similarities and Differences Among Genomes. *?* **?** (?): ?

85. Lander, Eric S. and David Botstein (1987). Homozygosity Mapping: A Way to Map Recessive Traits in Humans by Studying the DNA of Inbred Children. *Science* **236** : 1567-1570.

86. Lewis, Ricki (1993). New Gene Boutiques Spurred by HGP Promise to Represent Biotechnology's Second Coming. *Genetic Engineering News* **16** (15 September): 1, 8, 29.

87. Maxam, Allan M. and Walter Gilbert (1977). A New Method for Sequencing DNA. *Proceedings of the National Academy of Sciences (USA)* **74** (February): 560-564.

88. McConnell, Bill (1993). Alliance in Genetic Research. *Daily Record* (24 May): 1, 7.

89. Melillo, Mark W. (1993). SmithKline Beecham Allies with HGS in Therapeutic Pact. *Genetic Engineering News* (15 June): 1, 20.

90. Mercator Genetics, Inc. (1993). Public information packet. 16 December. Mercator Genetics, Inc., sent by Jeanne Gutfield, Administrative Assistant for Dennis Drayna.

91. Michelinie, Susan E. (1994). Press release: Collaborative Research Applauds NIH Decision to Drop DNA Gene Fragment Patent Applications. 17 February. Collaborative Research, Inc.

92. Millennium Pharmaceuticals, Inc. (1993). Fact Sheet. Fall. Millennium Pharmaceuticals, Inc.

93. Millennium Pharmaceuticals, Inc. (1993). Press release: Top Genome Scientists Form Biotechnology Company to Identify Disease-Causing Genes for Therapeutic Development. 4 August. Millennium Pharmaceuticals, Inc.

94. Millennium Pharmaceuticals, Inc. (1993). Public information sheet: The Scientific Team. Fall. Millennium Pharmaceuticals, Inc.

95. Miyata, Mitsuru (1994). Ohtsuka Pharmaceutical Company to Develop Diagnostic Medicine, Therapeutic Medicine, and Food Based on DNA Analysis. *Nikkei Biotechnology* (17 Janaury): kindly translated by Foreign Broadcast Information Service.

96. Miyata, Mitsuru. (1994). Phone interview. 2 February. Nikkei Biotechnology.

97. Morgenthaler, Lissa (1993). Just What the Doctor Ordered: Gene Therapy Is Now Stuff of Dollars, Not Just Dreams. *Barron's* **73** (20 September): 10-11, 31.

98. Myriad Genetics, Inc. (1993). Executive Summary. 1 March. Myriad Genetics, Inc.

99. Myriad Genetics, Inc. (1993). Fact Sheet. Myriad Genetics, Inc.

100. Nash, J. Madeline (1993). How Did Life Begin? *Time* (11 October): 68-74.

101. Nelson, Stanley F., John H. McCusker, Mark A. Sander, Yun Kee, Paul Modrich and Patrick O. Brown (1993). Genomic Mismatch Scanning: A New Approach to Genetic Linkage Mapping. *Nature Genetics* **4** (May): 11-18.

102. Nikkan Kogyo Shimbun (1994). Kazusa DNA Research Institute at the Kazusa Academia Park. *Nikkan Kogyo Shimbun* (19 January): kindly translated by the Foreign Broadcast Information Service.

103. Park, Tae Kwo, Qing Feng and Julius Rebek (1992). Synthetic Replicators and Extrabiotic Chemistry. *Journal of the American Chemical Society* **114** (No. 12): 4529-4532.

104. Peterson, Lisa. (1994). Letter to Robert Cook-Deegan, OTA contractor, along with copy of draft contract report marked up by Randal Scott and Roy Whitfield of Incyte. 24 February. Incyte Pharmaceuticals, Inc.

105. Potera, Carol (1993). GMS May Speed Linkage Mapping. *Genetic Engineering News* **13** (1 June): 1?

106. Potera, Carol (1993). In Vitro Evolution Creates Novel Drugs. *Genetic Engineering News* (15 April): 1.

107. Potter, Ray (1993). Cashing In on the Human Genome. *BioWorld Financial Watch* **1** (5 September): 1-2.

108. Pramik, Mary Jean (1993). Human Genome Project Spins Off Array of Novel Methods and Technologies. *Genetic Engineering News* **13** (15 September): 6.

109. Reynolds, Sherry L. (1994). Letter to Robert Cook-Deegan, OTA contractor, and copy of draft marked by Millennium corporate officers. 22 February. Millennium Pharmaceuticals, Inc.

110. Richard, John P. (1993). Press release: Collaborative Research, Inc., and Harvard Medical School Sign Exclusive License for Multiplex Seqeuncing. 29 November. Collaborative Research, Inc.

111. Roberts, Leslie (1991). DOE's Genome Project Comes of Age. *Science* **252** (26 April): 498-501.

112. Roberts, Leslie (1993). Galas to Leave DOE for Biotech Company. *Science* **260** (25 June): 1867.

113. Sagami Chemical Research Center. (1991). Fact sheet: 3-Year Project: Throwing Light on Human Proteins. Sagami Chemical Research Center.

114. Sagami Chemical Research Center. (1993). Informational brochure on the Center. Sagami Chemical Research Center, Kanagawa, Japan.

115. Sandburg, Brenda (1993). Sequana Partnership to Map Osteo Genes. *BioWorld Today* **4** (No. 169, 31 August): 1.

116. Sandburg, Brenda (1993). Sequana, Alopex Team Up to Map Baldness Genes. *BioWorld Today* **4** (177, 13 September): 1.

117. Schultz, Tammy. (1994). Letter to Robert Cook-Deegan, OTA contractor, along with draft contract report marked up by Peter Meldrum, President of Myriad Genetics, Inc. 16 February. Myriad Genetics, Inc.

118. Sequana Therapeutics. (1993). Fact Sheet: Corporate Background. 1-9. Sequana Therapeutics, Inc.

119. Sequana Therapeutics. (1993). Fact Sheet: Scientific Advisory Board. 1-5. Sequana Therapeutics, Inc.

120. Sequana Therapeutics. (1993). Press release: Sequana Appoints Vice President of Research and Development. 7 October. Sequana Therapeutics, Inc.

121. Sequana Therapeutics. (1993). Press release: Sequana Therapeutics and Jackson Laboratory Announce Collaboration to Study Genetic Causes of Obesity. 29 June. Sequana Therapeutics, Inc.

122. Sequana Therapeutics, Inc. (1993). News release: Sequana and Alopex to Map Genes for Common Disorders. 13 September. Sequana Therapeutics, Inc.

123. Sequana Therapeutics, Inc. (1993). News release: Sequana Therapeutics and Southwest Foundation to Map Genes Associated with Osteoporosis. 30 August. Sequana Therapeutics, Inc.

124. Suguwara, Sandra (1992). Nurturing High Tech. *Washington Business, Washington Post* (12 October): 1, 20-21.

125. Sutherland, Daniel (1993). Looking for a Cash Cure. *Washington Business, Washington Post* (23 August): 1, 14-15.

126. Swinbanks, David (1993). Institute Files for Patents on First Japanese Sequences. *Nature* **361** (18 February): 576.

127. Technical Insights, Inc. (1993). Company to Watch. *Genetic Technology News, Section of Biotechnology Information Package* **13** (November):

128. The Institute for Genomic Research. (1994). Information brochure. The Institute for Genomic Research.

129. Tsui, Lap-Chee, Manuel Buchwald, et al. (1985). Cystic Fibrosis Locus Defined by a Genetically Linked Polymorphic DNA Marker. *Science* **230** (29 November): 1054-1057.

130. van Brunt, Jennifer (1993). Incyte Gets Third Patent for BPI. *BioWorld Today* **4** (26 August): 1.

131. van Brunt, Jennifer (1993). New Company Sequana Studies Obesity in Mice. *BioWorld Today* **4** (No. 125, 29 June): 1.

132. van Brunt, Jennifer (1993). Scientists Embark on New Millennium. *BioWorld Today* **4** (4 August): 1.

133. Venter, J. Craig. (1992). Letter to Senator Dennis DeConcini. 1 December. From The Institute for Genomic Research to the Committee on the Judiciary, US Senate.

134. Venter, J. Craig. (1992). Statement of J. Craig Venter, Ph.D., President and Director, The Institute for Genomic Research, Before the Subcommittee on Patents, Copyrights, and Trademarks, Senate Judiciary Committee. 22 September. Serial No. J-102-83. Committee on the Judiciary, US Senate.

135. Vovis, Gerald F. (1993). Press release: Collaborative Research Awarded Genomic Research Grants and Contracts Totalling $2,000,000. 16 December. Collaborative Research, Inc.

136. Vovis, Gerald F. (1994). List of federal grants and contracts. 28 February. Collaborative Research, Inc.

137. Wada, Akiyoshi. (1993). Fax message to Robert Cook-Deegan. 24 December. Sagami Chemical Research Center.

138. Wade, Nicholas (1994). A Bold Short Cut to Human Genes. *New York Times* (22 February): C1, C9.

139. Washington FAX (1994). NIH Will Not Appeal Patent Rejections on cDNA. *Washington FAX* (11 February): 1.

140. Yang, Dori Jones (1992). Lighting a Fire at Camp DNA. *Business Week* (16 November): 73, 76.