Harvard Journal of Law & Technology
Volume 17, Number 2 Spring 2004

RECENT DEVELOPMENTS

Columbia, Co-transformation, Commercialization & Controversy
The Axel Patent Litigation

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> "WHEN WE SPLICED THE PROFIT GENE INTO ACADEMIC CULTURE, WE CREATED A NEW ORGANISM — THE RECOMBINANT UNIVERSITY. WE REPROGRAMMED THE INCENTIVES THAT GUIDE SCIENCE. THE RULE IN ACADEME USED TO BE 'PUBLISH OR PERISH.' NOW BIOSCIENTISTS HAVE AN ALTERNATIVE — 'PATENT AND PROFIT.'" TOM ABATE[1]

Eight biotechnology and pharmaceutical companies have recently sued Columbia University, alleging Columbia's current patent on technology that enables production of many modern protein-based drugs is invalid and unenforceable. Though researchers at Columbia developed the ground-breaking technology in the late 1970s and early 1980s, the patent-in-suit was actually issued in September 2002. This case has achieved some notoriety because it is the first example of a university mimicking a pharmaceutical company in aggressively attempting to prolong patent protection,[2] and therefore has stirred controversy surrounding the doctrine of university commercialization.

I. HISTORICAL AND SCIENTIFIC BACKGROUND

In the 1960s and 1970s, the research of Professors Herbert W. Boyer, Stanley N. Cohen, and Paul Berg led to the seminal discoveries that would spawn the biotechnology revolution.[3] Berg invented recombinant DNA technology, which is the process of constructing a DNA "molecule containing parts of DNA from different species."[4] This breakthrough allowed scientists to manipulate genes and spawned innumerable practical applications,[5] most notably through transformation, which modifies a host cell's genome through introduction of exogenous DNA from a foreign cell.

The transformation technique elicited significant academic interest, as it better allowed scientists to study the functional

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1. Tom Abate, *Scientists' 'Publish or Perish' Credo Now 'Patent and Profit'; 'Recombinant U.' Phenomenon Alters Academic Culture*, S.F. CHRON., Aug. 13, 2001, at D1 (discussing interview with Paul Berg, recipient of the 1980 Nobel Prize in Chemistry).

2. *See Ownership at Too High a Price?*, 21 NATURE BIOTECH. 953, 953 (2003).

> It's a story of greed, legal wrangling, and political intrigue . . . . For once, the story does not center on a secretive biotechnology corporation bent on world domination. It focuses instead on a center of learning, New York's Columbia University, which apparently is bent on dominating biotechnology research through patents issued in the early 1980s . . . .

Id.

3. *See* Lasker Found., Former Award Winners, Basic Medical Research 1980, *available at* http://www.laskerfoundation.org/awards/library/1980basic.shtml (last visited Mar. 29, 2004); *see also* U.S. Patent No. 4,237,224 (issued Dec. 2, 1980); U.S. Patent No. 4,468,464 (issued Aug. 28, 1984); U.S. Patent No. 4,740,470 (issued Apr. 26, 1988).

4. The Royal Swedish Acad. of Sci., Press Release: The 1980 Nobel Prize in Chemistry (Oct. 14, 1980), *available at* http://www.nobel.se/chemistry/laureates/1980/press.html.

5. *See id.*

molecular biology of DNA and genes.[6] However, the true power of transformation was that it allowed scientists to convert normal cells into microscopic protein-producing "factories." In the late 1970s, when molecular biology was relatively primitive, transformation technology was limited to using plasmids[7] to deliver the foreign DNA; even after successful transformation, the plasmid would be lost over a few generations of bacterial replication.[8] Most plasmid-based transformation was limited to transforming prokaryotes (cells without nuclei), despite the significant interest in producing proteins from eukaryotes (cells with nuclei, such as those in humans, mice, etc.) including insulin, antibodies, and growth hormones. Such eukaryotic proteins are, in general, extensively modified with various sugar linkages and packaged in certain subcellular components; prokaryotic cells lack the machinery to perform these functions. An additional obstacle is that even if a eukaryotic protein were produced in bacteria, it would be very difficult to totally purify it from the massive quantities of bacterial endotoxin, a highly antigenic lipoprotein. Thus, eukaryotic proteins must be produced in eukaryotes. However, few early transformation experiments were dedicated to eukaryotes, and all transformation procedures were plagued by a lack of reproducibility, low transformation efficiency (less than 0.01% chance of successful transformation), and the fact that the successful transformants could not be isolated from the non-transformants.[9]

Between 1977 and 1981, Professor Richard Axel and his federally funded collaborators[10] at Columbia University revolutionized the practice of transformation with their development of co-transformation, the simultaneous transformation of a eukaryotic cell's

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6. *See* Angel Pellicer et al., *Altering Genotype and Phenotype by DNA-Mediated Gene Transfer*, 209 SCI. 1414, 1414–15 (1980) (noting that "transformation provides an in vivo assay for the functional role of DNA sequence organization about specific genes").

7. Plasmids are small circular extrachromosomal pieces of DNA that replicate independently of the chromosome. *See* Giuseppe F. Miozzari, *Strategies for Obtaining Expression Peptide Hormones in* E. coli, *in* INSULINS, GROWTH HORMONE, AND RECOMBINANT DNA TECHNOLOGY 15 (John L. Gueriguian et al. eds., 1981).

8. As extrachromosomal DNA, the plasmids would generally be lost after a few generations of bacterial replication, in part because there was no energetic or evolutionary advantage that would accrue to the bacteria if it used precious DNA precursors to synthesize and maintain new plasmids. *Cf.* Angel Pellicer et al., *The Transfer and Stable Integration of the HSV Thymidine Kinase Gene into Mouse Cells*, 14 CELL 133, 140 (1978) (noting requirements necessary for survival of independent extrachromosomal DNA).

9. *See* Elizabeth H. Szybalska & Waclaw Szybalski, *Genetics of Human Cell Lines, IV: DNA-Mediated Heritable Transformation of a Biochemical Trait*, 48 PROC. NAT'L ACAD. SCI. 2026, 2026–27 (1962) (discussing the problems of transformation and reporting some solutions to those problems resulting from "the discovery of highly selective genetic markers"); *see also* Pellicer et al., *supra* note 8, at 140.

10. Axel's work was funded by two grants from the NIH. *See* U.S. Patent No. 4,399,216 (issued August 16, 1983); *see also* CRISP Database, NIH Grant Numbers CA-23767, CA-76346, *at* http://crisp.cit.nih.gov/ (last visited Mar. 10, 2004).

genotype with two different foreign DNA molecules.[11] One DNA molecule (hereinafter "DNA I") would be the gene coding for the desired proteinaceous material, and the other DNA molecule (hereinafter "DNA II") would be a gene for a selectable marker. A selectable marker is a particular gene that provides a cell with a necessary biological tool to survive and overcome a biological hardship, such as deprivation of a nutrient or the presence of an antibiotic. Therefore, experimental conditions could be designed such that only co-transformed "protein factory" cells — i.e., those that could both produce the desired proteinaceous material and survive the biological hardship — would be isolated. Selectable markers are generally amplifiable, meaning that in response to increasingly strenuous conditions, the cells that produce the most foreign DNA would be most likely to survive.

The presence of the selectable marker solved the problem of identification and isolation of successful transformants because non-transformed cells perished. Co-transformation also solved the problem of insufficient protein production by designing recombinant DNA I such that it would integrate into the chromosome of a host cell, and thus persist even after hundreds of generations. Moreover, the selectable marker would allow amplification of a piece of DNA I/DNA II, as the host cell sought to survive in the experimentally-induced harsh conditions.[12]

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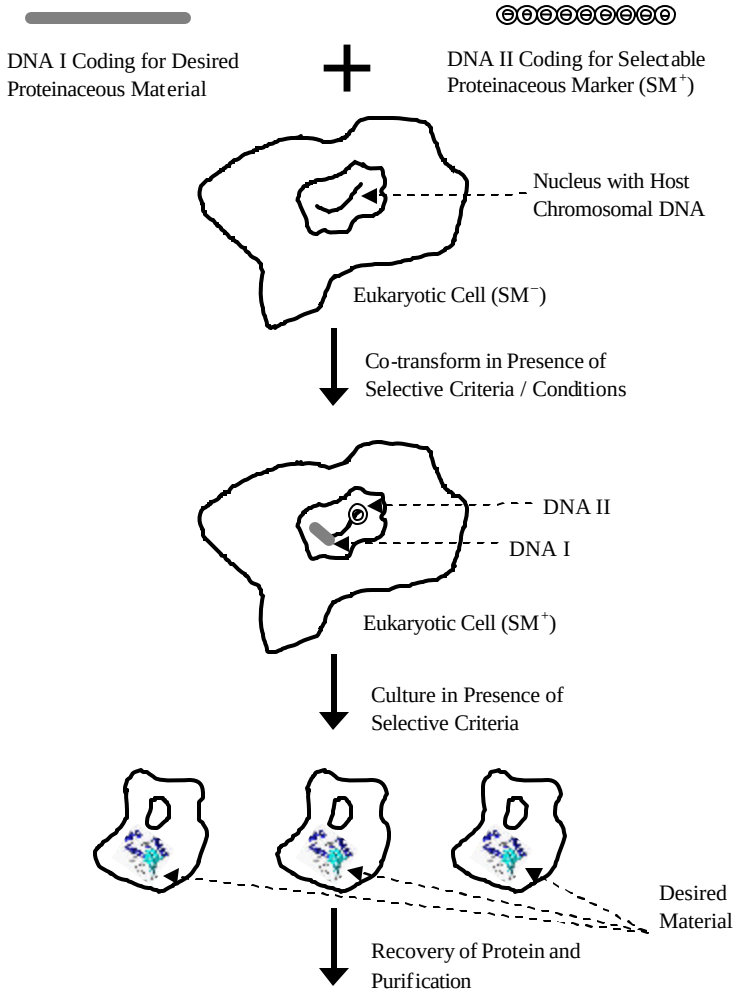
11. *See, e.g.*, M. Wigler et al., *Transformation of Mammalian Cells with an Amplifiable Dominant-Acting Gene*, 77 PROC. NAT'L. ACAD. SCI. 3567 (1980) (prokaryote DNA to eukaryote host); Pellicer et al., *supra* note 8, at 133, 139 (viral gene to eukaryote host); B. Wold et al., *Introduction and Expression of a Rabbit ß-Globin Gene in Mouse Fibroblasts*, 76 PROC. NAT'L. ACAD. SCI. 5684, 5687–88 (1979) (eukaryote gene to eukaryote host). *See generally* Richard Axel, *Axel Lab Publications*, *at* http://cpmcnet.columbia.edu/dept/neurobeh/axel/research.html (last visited Mar. 10, 2004).

12. *See* Diane M. Robins et al., *Transforming DNA Integrates into the Host Chromosome*, 23 CELL 29, 29, 36–37 (1981) (stating that the selectable marker and DNA I "are found covalently linked in the transformed cell," become stably integrated, and allow "amplification of selectable markers with nonselectable cotransformed genes"); *see also* Pellicer et al., *supra* note 6, at 1421.

Figure 1: The Scheme of Co-Transformation
(Developed by Professor Axel)



Two DNA molecules, with DNA I coding for the desired proteinaceous material and DNA II coding for a selectable marker, are introduced into a eukaryotic cell. The cell initially contains no selectable marker (hence the SM^- designation) but does contain the marker after co-transformation (SM^+). The SM^+ cells thrive in the selective media while other, non-transformed SM^- cells die. Co-transformed cells use DNA I to synthesize the desired protein product, which can be recovered and purified.[13]

13. Adapted from U.S. Patent No. 4,399,216 (issued Aug. 16, 1983). The depicted proteinaceous material is a representation of the yeast Cdc-13 DNA binding domain, adapated from Rachel M. Mitton-Fry et al., *Conserved Structure for Single-Stranded Telomeric DNA Recognition*, 296 SCI. 145, 145 (2002).

A. The Axel Patent

An abstract of one of Axel's important papers hinted at the awesome power thus unlocked: "The use of this [process] may allow the introduction and amplification of virtually any [genetic or protein] element in various new cellular environments."[14] Columbia University quickly seized on Axel's work and on February 25, 1980 filed a patent application resulting in U.S. Patent No. 4,399,216, issued August 16, 1983 ("'216 patent" or "Axel patent"). The '216 patent describes the invention as a process for inserting DNA into eukaryotes to yield transformed cells with foreign DNA integrated into chromosomal DNA which can sustainably generate functional proteins, and lists seventy-three claims, as summarized here:

- A process for co-transforming a suitable eukaryotic host cell with one or multiple copies of DNA I and DNA II, which can be either linked or unlinked, where DNA I may be a proteinaceous material that incorporates into the host cell chromosome and DNA II is the selectable marker.[15]

- The scope of the claim "suitable eukaryotic host cell" is tapered by dependent claims defining the term as a mammalian cell, which itself is further delimited to either an erythroblast (red blood cell precursor) or a fibroblast (connective tissue precursor).[16]

- The scope of the claim "proteinaceous material" is tapered by dependent claims defining the term as interferon protein, insulin, growth hormone, clotting factor, viral antigen, antibody, or enzyme.[17]

- The scope of the claim "DNA II" is tapered by dependent claims for the gene for thymidine kinase, the gene for adenine phosphoribosyltransferase, or a gene for drug resistance, which includes antibiotic

14. Wigler et al., *supra* note 11, at 3567.
15. *See* U.S. Patent No. 4,399,216 (issued Aug. 16, 1983) claims 1, 2, 22, 27, 28, 31, 48, 54, 55, 71.
16. *See id*. claims 12–14, 20, 21, 24, 42–44, 65–67.
17. *See id*. claims 3–8, 23, 32–38, 52, 56–61.

resistance genes and a dependent claim for dihydrofolate reductase.[18]

- A process for detecting and identifying eukaryotic cells successfully transformed based on their selectable phenotype, as well as recovering these cells.[19]

- A process for culturing the transformed cell to yield a multiplicity of such cells. A process by which the culture is grown in increasing amounts of an agent that exerts selective pressures, such that DNA II will be amplified and transformants can be identified.[20]

- A process for producing proteinaceous material and recovering this protein.[21]

- A claim for the cell, eukaryotic or mammalian, into which DNA I has been incorporated into the host cell's genome. Also, a claim for the cell, eukaryotic or mammalian, into which DNA I, in the case where DNA I and DNA II were linked, has been incorporated into the host cell's genome.[22]

The written description of the Axel patent is substantial, fully disclosing background prior art of recombinant DNA as well as the experimentation undertaken by Axel and colleagues, as necessary to define the scientific protocol to a person reasonably skilled in molecular biology in 1980. The written description expressly discloses the embodiments of co-transforming multiple copies of DNA I linked to an amplifiable DNA II, identifying and culturing transformed cells, and obtaining large quantities of proteinaceous material.[23] The preferred embodiment is to use DNA I and DNA II attached to phage DNA, which is encapsulated in the viral particle before co-transformation.[24]

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18. *See id*. claims 16–19, 46, 47, 69, 70.
19. *See id*. claims 25, 26.
20. *See id*. claims 22, 54.
21. *See id*. claim 51.
22. *See id*. claims 49, 50, 72, 73.
23. *See id*., col. 3, ll. 42–68.
24. *See id*., col. 5, ll. 51–57. Phages are viruses capable of delivering DNA to target cells, commandeering those target cells, and using them to replicate viruses, which then attack new target cells. *See* BRUCE ALBERTS ET AL., MOLECULAR BIOLOGY OF THE CELL 275 (3d ed. 1994).

It was quite ambitious for Columbia in February 1980 to even claim a living cell in its patent application, since the Supreme Court did not decide whether genetically modified organisms were patentable subject matter until June 1980.[25] In *Diamond v. Chakrabarty*, the Court held that a living organism that (a) was entirely a product of human ingenuity and (b) possessed new characteristics that could not be found in nature constituted either a properly patentable manufacture or composition of matter under 35 U.S.C. § 101.[26] Chakrabarty's patent claimed both a strain of *Pseudomonas* bacteria that degraded octane and the process he used to create the *Pseudomonas*.[27] The subject matter of Columbia's patent was quite similar to the one at issue in *Chakrabarty*, as both claimed a genetically enhanced cell and the process to create the cell.

Regardless of whether the Axel patent could even be successfully prosecuted, Columbia could not have been assured of ultimately obtaining title to the invention. In the 1960s and 1970s, there was substantial disagreement within the federal government over the propriety of transferring to private entities the title to inventions developed via public subsidy.[28] The Bayh-Dole Act, enacted on December 12, 1980, was designed as a means to resolve this debate, encouraging commercialization of research by allowing universities to take title to inventions produced with federal funding.[29] As Columbia's patent predated Bayh-Dole by ten months, Columbia was required to enter into an agreement with the National Institutes of Health ("NIH") to take title to the inventions described in the Axel patent. The agreement allowed Columbia to license the technology, provided that those licenses specifically "include[d] adequate safeguards against unreasonable royalties and repressive practices" and guaranteed that royalties "not in any event be in excess of normal trade practice."[30]

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25. Diamond v. Chakrabarty, 447 U.S. 303 (1980).

26. *See id*. at 310.

27. *See id*. at 305–06.

28. *See* Univ. of Cal. Office of Tech. Transfer, The Bayh-Dole Act: A Guide to the Law and Implementing Regulations (Sept. 1999), *available at* http://www.ucop.edu/ott/bayh.html.

29. *See* The Patent and Trademark Law Amendments (Bayh-Dole) Act, 35 U.S.C. §§ 200–12 (2000); *see also* Univ. of Cal. Office of Tech. Transfer, *supra* note 28; Jane Larson, *Tech Transfer on Table,* ARIZ. REPUBLIC, Jan. 12, 2003, at D1; *Innovation's Golden Goose*, THE ECONOMIST, Dec. 14, 2002, at 3.

30. Ted Agres, *Columbia Patents Under Attack* (July 25, 2003), *at* http://www.biomedcentral.com/news/20030725/03.

B. The Biotechnology Revolution: Protein-Based Pharmaceuticals and the Axel Patent

Enterprising scientists in the 1970s and 1980s decided to exploit the emergent field of molecular biology as an alternative to the prevailing model of producing drugs by chemical synthesis. Genentech was co-founded in 1976 by Professor Herbert Boyer and immediately undertook the task of producing sufficient quantities of human proteins for use as pharmaceutical agents; its early projects included insulin, growth hormone, a clotting factor, and an interferon.[31] Amgen was founded in 1980 and sought to develop its products based on recent "advances in recombinant DNA and molecular biology."[32] The successful efforts of Amgen, Genentech, and others in the burgeoning biotechnology industry revolutionized the entire notion of pharmaceuticals and expanded the paradigm of drug development from the classic small molecule model to include protein-based drugs like insulin, antibodies, and enzymes:

> Biotechnology's unique approach to making pharmaceuticals has been to use human proteins as drugs rather than the chemicals of traditional pharmaceuticals . . . . The first step in the manufacturing of [a desired proteinaceous product] is to genetically engineer a cell so that it produces the [desired proteinaceous product]. This requires introducing the genetic information, or DNA, that provides the cell with the instructions it needs to produce [the proteinaceous product]. Once a cell has been engineered to express the product, it is used to establish a cell line [and then used to grow a large quantity of the protein].[33]

The Axel patent was instrumental in facilitating the development of a number of modern protein-based drugs expressed in eukaryotic vectors.[34] Columbia licensed the Axel patent to over thirty

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31. *See* Genentech, *Corporate Chronology*, *available at* http://www.gene.com/gene/about/corporate/history/timeline/index.jsp (last visited Jan. 31, 2004).

32. Amgen, Inc., *Amgen Backgrounder*, *available at* http://www.amgen.com/corporate/AboutAmgen/backgrounder.html (last visited Feb. 14, 2004).

33. Genentech, *Manufacturing Xolair (Omalizumab) for Subcutaneous Use*, *at* http://www.gene.com/gene/products/information/immunological/xolair/development.jsp (last visited Mar. 24, 2004).

34. *See, e.g.*, Ken Howard, *Biotechs Sue Columbia over Fourth Axel Patent*, 21 NATURE BIOTECH. 955, 955 (2003); *Ownership at Too High a Price?*, *supra* note 2, at 953. Note that due to other aspects of genetic engineering, protein structure, and protein purification technology, some protein drugs can be produced in bacterial vectors, especially in the bacterium *Escherichia coli*. Drugs produced in *E. coli* include Amgen's Neupogen, Leukine,

companies,[35] including Genentech, Amgen, Immunex,[36] Genzyme, Abbott, Biogen,[37] Wyeth,[38] Baxter, and Serono, thus directly contributing to the successful development of at least twenty-nine drugs by these companies[39] as shown in Appendix A, *infra*. Several observations regarding this sub-group of protein-based drugs are noteworthy:

(1) Twenty-three of the twenty-nine drugs are in categories claimed by the Axel Patent:[40] nine drugs are antibodies or antibody

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and Kineret; Genentech's Nutropin (all variants), Actimmune, and Protropin; Wyeth's Neumega; Lilly's Humatrope and Humalog; Chiron's Proleukin and Betaseron; Schering-Plough's Intron A, PEG-Intron, and Rebetron; Johnson & Johnson's Retavase and Natrecor; and Aventis' Lantus. *See generally* Gary Walsh, *Biopharmaceutical Benchmarks — 2003*, 21 NATURE BIOTECH. 865 (2003); Centocor, Inc., Retavase (reteplase) U.S. Prescribing Information (Nov. 2000), *available at* http://www.centocor.com/pi/retavasePI_11-00A.pdf; Scios, Inc., Natrecor (nesiritide) U.S. Prescribing Information (Oct. 2003), *available at* http://www.sciosinc.com/pdf/natrecorpi_final.pdf. Additionally, Wyeth's Mylotarg is produced in the bacterium *Micromonospora echinospora* ssp. calichensis. *See* Wyeth Labs., Mylotarg (gemtuzumab ozogamicin) U.S. Prescribing Information, *available at* http://www.wyeth.com/content/ShowLabeling.asp?id=119 (last visited Mar. 10, 2004).

35. *See Paying Twice?*, 2 NATURE DRUG DISCOVERY 690 (2003); Complaint at ¶21, Genentech, Inc. v. Tr. of Columbia Univ. (N.D. Cal. 2003) (No. 3:03-cv-01603) [hereinafter "Genentech Complaint"]; Complaint, Immunex, Inc. and Amgen, Inc. v. Tr. of Columbia Univ. (C.D. Cal. 2003) (No. 2:03-cv-04349) [hereinafter "Amgen Complaint"]; Complaint at ¶¶ 3, 5, 7, 9, 24, Biogen, Inc., Genzyme Corp., and Abbott Bioresearch Ctr., Inc. v. Tr. of Columbia Univ. (D. Mass. 2003) (No. 03-cv-11329-MLW) [hereinafter "Biogen Complaint"]; Complaint at ¶ 2, Wyeth, et al., v. Tr. of Columbia Univ. (D. Mass. 2003) (No. 03-cv-11570-MLW) [hereinafter "Wyeth Complaint"]; Complaint at ¶ 6, Baxter Healthcare Corp. v. Tr. of Columbia Univ. (D. Mass. 2003) (No. 03-cv-12221-MLW) [hereinafter "Baxter Complaint"]; Complaint at ¶7, Serono, Inc. v. Tr. of Columbia Univ. (D. Mass. 2003) (No. 03-cv-12401-MLW) [hereinafter "Serono Complaint"]; *see also* Herbert Pardes, *Molecular Genetics at Columbia*, 1 BIOMEDICAL FRONTIERS (Winter 1994), *available at* http://cpmcnet.columbia.edu/news/frontiers/archives/biomed_v1n2_0002.html.

36. Immunex Corporation had licensed the Axel patent, but was acquired by Amgen in July 2002. *See* Amgen, Inc., *supra* note 32. Immunex was named as a joint plaintiff on the Amgen Complaint.

37. Biogen merged with Idec Pharmaceuticals in November 2003 to form Biogen Idec. *See* Biogen Idec, *Company*, *available at* http://www.biogen.com/site/013.html (last visited Feb. 14, 2004).

38. Columbia originally licensed the Axel patent to The Genetics Institute, Inc., and this license was extended to Wyeth when the successor to The Genetics Institute, Inc., became a wholly-owned subsidiary of Wyeth. *See* Wyeth Complaint, *supra* note 35, ¶¶ 2, 5.

39. Approximately ninety recombinant protein pharmaceuticals are approved for use in the U.S. *See generally* Walsh, *supra* note 34. Virtually every major pharmaceutical company markets at least one recombinant protein product in the United States, including Pfizer (Rebif, Somavert), Merck (recombinant vaccines Recombivax HB and Comvax), and GlaxoSmithKline (recombinant vaccines Engerix-B, Pediarix, and Twinrix). *See, e.g.*, Pfizer, Inc., Medicines & Products, *available at* http://www.pfizer.com/do/medicines/mn_uspi.html (last visited Mar. 31, 2004); Merck & Co., Inc., Vaccine and Disease Information, *available at* http://www.merckvaccines.com/vaccineInfo_frmst.html (last visited Mar. 31, 2004); GlaxoSmithKline PLC, Vaccines, *available at* http://www.gsk.com/products/vaccines.htm (last visited Mar. 31, 2004).

40. *See supra* text accompanying note 17.

derivatives, seven are enzymes, four are clotting factors, two are interferons, and one is a growth hormone.[41]

(2) A number of the drugs in Appendix A are recent developments: Avastin, for example, was approved by the Food and Drug Administration ("FDA") in February 2004. Advate, Aldurazyme, Amevive, Fabrazyme, Raptiva, and Xolair were approved in 2003, and others including Humira, Rebif, and Zevalin received approval in 2002. A number of additional novel protein drugs are in late stages of development or are pending approval as of the publication of this Note.[42]

(3) Of the twenty-nine drugs, twenty-eight have been confirmed to have used the Chinese hamster ovary ("CHO") cell[43] as a mammalian expression system that reliably produces large quantities of the relevant glycoproteins.

(4) Nine drugs (Activase, Avastin, Cathflo Activase, Herceptin, Pulmozyme, Raptiva, Rituxan, TNKase, and Xolair) expressly document the use of an antibiotic in the culture medium for growth of transformed cells, as described in the Axel patent, while six (Enbrel, Epogen, Procrit,[44] Rebif, Ovidrel, and Gonal-f[45]) are otherwise known to be directly based on the Axel patent. However, it is almost certain that all use some selective agents in culturing their transformed cells in accordance with the Axel patent.[46]

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41. Note that of the other six products, three are erythropoietins, one is thyroid stimulating hormone, one is human chorionic gonadotropin, and one is follicle stimulating hormone.

42. *See* Walsh, *supra* note 34, at 868 (estimating 500 candidate biopharmaceuticals are in development); PHARM. RESEARCH AND MFRS. OF AM., NEW MEDICINES IN DEVELOPMENT: BIOTECHNOLOGY (Sept. 27, 2002), *available at* http://www.phrma.org/newmedicines/resources/2002-10-21.93.pdf (listing 371 biotechnology medicines in development).

43. CHO cells are used in molecular biology laboratories for study and expression of proteins. *See* Am. Type Culture Collection, CHO-K1 Cell Line Catalog Detail, *at* http://www.atcc.org/SearchCatalogs/longview.cfm?view=ce,419766,CCL-61&text=cho (last visited Mar. 31, 2004). *See generally* Theodore T. Puck et al., *Genetics of Somatic Mammalian Cells. III. Long-term Cultivation of Euploid Cells from Human and Animal Subjects*, 108 J. EXPERIMENTAL MED. 945, 947, 949–50 (1958) (noting that CHO cell cultures are "particularly hardy and reliable" and grow in "continuous cultivation for more than 10 months with no diminution in growth rate or change in . . . morphology," and that the CHO-K1 cell line arose from this experiment in 1958).

44. *See* Pardes, *supra* note 35.

45. *See* Serono Complaint, *supra* note 35, ¶¶ 6, 40.

46. *See generally* Genentech Complaint, *supra* note 35; Amgen Complaint, *supra* note 35; Biogen Complaint, *supra* note 35; Wyeth Complaint, *supra* note 35; Baxter Complaint, *supra* note 35. The fact that the drug companies are suing Columbia for patent invalidity suggests that their drugs did utilize Axel patent technology, even though the companies may not have fully disclosed their production processes. Note that all of the nine drugs that did explicitly disclose their reliance on the Axel patent in their prescribing information are Genentech drugs. The disclosure of the antibiotic is probably a result of Genentech's individual practice in drafting package inserts, as the other companies most likely also use selectable media in their co-transformation and production processes.

C. Columbia and the Axel Patent: Does Activism Signal Bad Faith or Defense of Intellectual Property?

Columbia's licensing of the Axel patent has become legendary, such that it is cited as the University's "single most successful innovation."[47] Columbia has collected license fees of $70 million from Genentech, $35 million from Biogen, $27 million from Wyeth, $25 million from Genzyme, $6 million from Serono, and $5 million from Baxter.[48] Between 1983 and 2002, it is estimated that the Axel patent generated some $400 million in aggregate revenue for Columbia.[49] The pace of licensing increased over time, and its licenses were generating approximately $100 million per year[50] in 2000 (the year it was set to expire) out of the $139 million in total technology transfer royalties generated by Columbia University as a whole.[51] These figures show Columbia was the most successful university in technology transfer in the years before expiration of the Axel patent[52]; the 2001 Association of University Technology Managers Licensing Survey found that North American universities, hospitals, and research institutions in aggregate collected $1.071 billion in licensing royalties and fees on 13,000 patents, and Columbia captured almost ten percent of that total based on *one* patent.[53]

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47. *Technology Office Renamed as License Income Rises*, COLUM. UNIV. REC., Oct. 14, 1994, *available at* http://www.columbia.edu/cu/record/archives/vol20/vol20_iss6/record2006.16.html; Genentech Complaint, *supra* note 35, ¶ 21; *see also* Ronald I. Eisenstein & David S. Resnick, *Going for the Big One: Blockbuster Patents Enrich University Coffers, But Can Also Affect Future Patenting and Research Decisions*, 19 NATURE BIOTECH. 881, 881 (2001) ("Successful university patents are usually judged not by the scope of the claims or the patent's subject matter (i.e., composition of matter, method of use, method of treatment, or method of synthesis) but rather on how much revenue the university has generated by licensing the patent.").

48. *See* Genentech Complaint, *supra* note 35, ¶ 21; Biogen Complaint, *supra* note 35, ¶¶ 5, 7; Wyeth Complaint, *supra* note 35, ¶ 2; Baxter Complaint, *supra* note 35, ¶ 5; Serono Complaint, *supra* note 35, ¶ 7.

49. *See* Ted Agres, *The Fruits of University Research*, 17 THE SCIENTIST 55 (July 14, 2003); Boston Univ. Cmty. Tech. Fund, Technology Transfer: Other Universities, *available at* http://www.bu.edu/ctf/transfer/success.html (last visited Mar. 13, 2004). Columbia's technology transfer enterprise has generated over $1 billion in total receipts, with nearly half coming from the Axel patent. *See* Larson, *supra* note 29.

50. *See* Agres, *supra* note 30.

51. Denise Gellene, *Genentech Sues Columbia over Biotech Patent*, L.A. TIMES., Apr. 18, 2003, at C2 (citing ASS'N OF UNIV. TECH. MANAGERS, AUTM LICENSING SURVEY 2001 (2003)).

52. *See* COLUMBIA UNIV. SCI. & TECH. VENTURES, ANNUAL REPORT 2000–2001 at 4, *available at* http://www.stv.columbia.edu/about/reports/annualreport2002.asp (last visited Apr. 10, 2004) (stating 2001 licensing revenue was $142.8 million, the third straight year in which Columbia had the "highest total technology licensing revenue of any U.S. research university"). Technically, the University of California was ranked first in technology transfer revenue for fiscal year 2001, but their ranking was the result of securing a one-time $200 million infringement settlement award from Genentech. *See* Agres, *supra* note 49.

53. *See* ASS'N OF UNIV. TECH. MANAGERS, AUTM LICENSING SURVEY: FY 2002, at 2, (2003), *available at* http://www.autm.net/surveys/02/2002spublic.pdf; Paul Elias, *Schools*

Columbia University quickly recognized the revenue potential of the Axel patent and embarked on an aggressive program to extend its duration as far as possible. Five days before the '216 patent issued in 1983, Columbia filed a divisional application[54] with the Patent and Trademark Office ("PTO"); this allowed continued prosecution of the '216 patent application by which Columbia ultimately secured a second patent, U.S. Patent No. 4,634,665 ("'665 patent") on January 6, 1987. On the basis of the '665 patent, Columbia filed additional divisional patent applications in 1986 (abandoned), 1989 (abandoned), and 1991, resulting in yet a third patent, U.S. Patent No. 5,179,017 ("'017 patent") issued on January 12, 1993. By the early 1990s, CHO had become quite well established as the mammalian vector of choice for expression of complex mammalian proteins.[55] Columbia thus introduced claim language specifically covering CHO cells into its 1991 application for the '017 patent as well as all subsequent applications. The PTO, however, did condition the grant of the '665 and '017 patents on a "terminal disclaimer," meaning that the duration of all three patents would terminate on the original termination date of the Axel patent, or August 16, 2000, in order to avoid double patenting of the same subject matter.[56] Columbia nevertheless filed

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Profit from Publicly Funded Research, CNN.COM (Apr. 29, 2003), *at* http://www.cnn.com/2003/EDUCATION/04/29/patent.universities.ap/index.html.

54. A divisional patent application arises when the original patent disclosed through an earlier patent application actually contained more than one invention. The later application for the independent invention, that discloses and claims only a part of the original invention, is called the divisional patent application. *See* MANUAL OF PATENT EXAMINING PROCEDURE § 201.06 (2003). The priority date and the term of the divisional patent, however, is generally the same as that of the original patent.

55. *See* S. Weikert et al., *Engineering Chinese hamster ovary cells to maximize sialic acid content of recombinant glycoproteins*, 17 NATURE BIOTECH. 1116, 1116 (1999) ("Recombinant glycoproteins produced by mammalian cells lines are currently being developed as therapeutics for a spectrum of diseases. Chinese hamster ovary (CHO) cells are widely used for this purpose."); Stanley Scheindlin, *Update on Biotechnology*, PHARMACY TIMES (May 2003), *available at* http://www.pharmacytimes.com/article.cfm?ID=433; Stephen Peuschen et al., *Genome to Factory*, *in* BIOMEDCITY, GRONINGEN, THE NETHERLANDS (Dec. 16, 2001), *available at* http://www.genomics.rug.nl/Expression_systems_BMCG.pdf. Few other recombinant protein drugs use a mammalian expression system different from CHO. For example, Johnson and Johnson's Remicade and the recently approved Erbitux from Imclone (in partnership with Bristol-Myers Squibb) are derived from murine cancer cell cultures. *See* Centocor, Inc., Remicade (infliximab) U.S. Prescribing Information (Apr. 1, 2003), *available at* http://www.remicade.com/PI/interactive_PI.jsp (citing David M. Knight et al., *Construction and Initial Characterization of a Mouse-Human Chimeric Anti-TNF Antibody*, 30 MOLECULAR IMMUNOLOGY 1443, 1444, 1449 (1993)); ImClone Systems, Inc., Erbitux (cetuximab) U.S. Prescribing Information, *available at* http://www.fda.gov/cder/foi/ label/2004/125084lbl.pdf (last modified Feb. 12, 2004). Serostim is derived from a murine C127 cell line. *See infra* note 190. Other protein drugs are simply extracted from human tissue cultures, such as Abbott's Abbokinase and Lilly's Xigris. *See* Abbott Labs., Abbokinase (urokinase) U.S. Prescribing Information, *available at* http://www.abbotthosp.com/prod/pdf/abbo.pdf (last visited Mar. 10, 2004); Eli Lilly & Co., Xigris (drotrecogin alfa) U.S. Prescribing Information (Nov. 14, 2003), *available at* http://pi.lilly.com/us/xigris.pdf.

56. *See* Agres, *supra* note 30.

continuation patent applications[57] on the '017 patent in 1992 (abandoned), 1994 (abandoned), and two on June 7, 1995. That date is quite significant, because on June 8, 1995, amendments to the US. patent law pursuant to the Uruguay Round Agreements of the General Agreement on Trade and Tariffs ("GATT") were slated to take effect.[58] This revision in the U.S. patent law would absolutely preclude this practice of continuation applications by rigidly capping the patent term at twenty years from the first priority date, regardless of the date of patent application.[59]

In early 2000, with time winding down on the life of the Axel patent and thus facing the prospect of losing a $100 million annual revenue source, Columbia turned to Congress for help. Specifically, the University sought out alumnus Judd Gregg, a Republican senator from New Hampshire.[60] Sympathetic to Columbia's plight, Senator Gregg argued that the provisions of the Hatch-Waxman Act[61] should apply to extend not only the patents of drugs delayed by FDA review, but also to patents on techniques used to make those drugs that could be delayed by FDA review: "[The Axel] patent should be eligible for patent extensions just like any other drug patent. This is an inequity my amendment addresses."[62] Such an argument is foreclosed not only by the language but also by the legislative history of the Hatch-Waxman Act.[63] The senator however inserted a provision to extend

57. *See generally* MANUAL OF PATENT EXAMINING PROCEDURE § 201.07 (2003) ("A continuation is a second application for the same invention claimed in a prior nonprovisional application and filed before the original becomes abandoned or patented.").

58. *See* Uruguay Round Agreements Act, Pub. L. No. 103-465, 108 Stat. 4809, § 532(a)(1) (1994) (codified at 35 U.S.C. § 154(c)(1) (2000)). GATT served as the precursor to the World Trade Organization.

59. *See* MANUAL OF PATENT EXAMINING PROCEDURE § 2701 (2003); *see also* Naomi Aoki, *Biotech Firms Sue Columbia University*, BOSTON GLOBE, July 16, 2003, at C1; Biogen Complaint, *supra* note 35, ¶22; Wyeth Complaint, *supra* note 35, ¶17; Baxter Complaint, *supra* note 35, ¶17. Prior to June 8, 1995, a utility patent's term would be the longer of seventeen years from issuance or twenty years from filing, whereas after June 8, 1995, the term was set at twenty years from filing. By filing on June 7, 1995, Columbia ensured that it could prosecute these two applications as far into the future as possible in order to obtain a new seventeen-year term from the date of issue of the future patent. *See Ownership at Too High a Price?*, *supra* note 2, at 953 ("Not willing to relinquish the [Axel] patents' riches, Columbia . . . set about filing a new patent in 1995 (by happy fortune one day before changes in U.S. patent law would make such an application impossible thereafter).").

60. *See* Agres, *supra* note 30; *Ownership at Too High a Price?*, *supra* note 2, at 953.

61. Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified in scattered sections of 15, 21, 28, and 35 U.S.C.).

62. Senator Judd Gregg (R-NH), *quoted in Congress Examines Biotech Patents*, CONTEMP. DIALYSIS & NEPHROLOGY, *available at* http://www.ikidney.com/iKidney/InfoCenter/Library/CDN/Archive/CongressExaminesBiotechPatents.htm (last visited Mar. 10, 2004).

63. In general, patent extension is available only to a product that is subject to regulatory review. Although 35 U.S.C. § 156(a)(5)(B) can permit extension of a patent claiming recombinant DNA in the manufacture of an FDA approved product, none of the Axel

the Axel patent into an unrelated agricultural appropriations bill.[64] The provision later became bundled into a military appropriations bill,[65] but ultimately was never enacted.[66]

At least at that time, Columbia officially conceded defeat, as a spokesperson stated that there was not a "next step in this patent extension story . . . there's just no way to go back after it expires."[67] In spite of the failure in Congress, Columbia maintained its efforts in prosecuting continuation applications, which paid off when one of the 1995 applications[68] resulted in the issuance of U.S. Patent No. 6,455,275 ("'275 patent") on September 24, 2002, more than two years after the original Axel patent expiration date. The PTO did not require any terminal disclaimer, meaning that the '275 patent would theoretically extend the patent rights until September 2019.[69] The '275 patent, like the '017 patent, explicitly claimed transformed CHO cells, thus putting some thirty biotechnology companies in jeopardy of paying seventeen additional years of royalties for technology that they

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patents claim any actual drug product along with its process of manufacture. *See* Hatch-Waxman Act, § 201(a), 98 Stat. at 1600–01 (codified at 35 U.S.C. § 156(a)(4), (5)(B) (1994)); H.R. REP. NO. 98-857, pt. 1, at 37–39 (1984) ("[T]he Committee on Energy and Commerce concluded on public policy and health policy grounds that only the first patent on a *drug-type product* should be extended" (emphasis added).); H.R. REP. NO. 98-857, pt. 2, at 8, 21–22 (1984) ("An extension for the recombinant DNA process patent is appropriate only when there are no product or use patents." In this case, of course, each of the plaintiff companies holds product patents on its drugs.); *see also* Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187, 191–92 (1999) (discussing potential revisions to Hatch-Waxman but mentioning nothing resembling the argument advanced by Senator Gregg). *But cf.* 148 CONG. REC. S7875–02 (daily ed. Aug. 1, 2002) (statement of Senator Hatch, discussing pharmaceutical research and noting changes wrought by the biotechnology revolution, asked "[i]f targeted patient populations get smaller and smaller and the production process patents become relatively more important than composition of matter patents, should [Congress] make process patents eligible for Waxman-Hatch partial patent term restoration?" However, as Senator Hatch was discussing process patents specific to producing a drug for a narrow patient base, this type of amendment would still not apply to the Axel patent, or similar patents, that claim fundamental, broadly applicable scientific tools).

64. *See* S. Res. 2536, 106th Cong. §2801 (2000); *see also* Julie Rovner, *Columbia University Amendment on Patent Extension*, CONGRESSDAILY, (May 12, 2000) *at* http://lists.essential.org/pipermail/pharm-policy/2000-May/000176.html. The move was immediately condemned by pharmaceutical industry groups, bioethicists, consumer groups, and other Congressmen including Senator John McCain and Representative Henry Waxman. *See* Bureau of National Affairs, *Columbia Cotransformation Patent Extension*, 5 HEALTH CARE DAILY (BNA) 7 (May 17, 2000).

65. *See* Bureau of National Affairs, *Some Senators Cry Foul Over Inclusion of Patent Extension Rider in Spending Bills*, 122 DAILY REPORT FOR EXECUTIVES A-41 (June 23, 2000).

66. *See* Eliot Marshall, *Depth Charges Aimed at Columbia's 'Submarine Patent,'* 301 SCI. 448 (2003).

67. Biogen Complaint, *supra* note 35, ¶ 29; *see also* Answer ¶ 29, Biogen, Inc., Genzyme Corp., and Abbott Bioresearch Ctr., Inc. v. Tr. of Columbia Univ. (D. Mass. 2003) (No. 03-cv-11329-MLW) [hereinafter "Answer to Biogen"].

68. The other 1995 application is still pending. *See* Biogen Complaint, *supra* note 35, ¶ 22.

69. See Table 1 for a summary of Columbia's co-transformation patents.

believed should have entered the public domain in 2000.[70] Columbia notified the biotechnology companies that it expected to continue to receive royalty payments.[71]

Table 1. Summary of History and Description of Columbia's Co-transformation Patents

PATENT	ISSUE DATE	EXPIRATION	HISTORY	CLAIMS
'216	Aug. 16, 1983	Aug. 16, 2000	Application for patent filed on Feb. 25, 1980	Co-transformation process with selectable marker; unlinked and linked DNA I and DNA II; protein production and recovery; transformed eukaryotic or mammalian cell
'665	Jan. 6, 1987	Aug. 16, 2000 (terminal disclaimer)	Divisional application filed on Aug. 11, 1983	Co-transformation process using phage or plasmid vehicle
'017	Jan. 12, 1993	Aug. 16, 2000 (terminal disclaimer)	Divisional application filed on June 18, 1991	Transformed CHO cell with DNA I stably integrated into chromosomal DNA
'275	Sept. 24, 2002	Sept. 24, 2019	Continuation application filed on June 7, 1995	DNA construct of DNA I / DNA II; DNA I encodes glycoprotein of interest; transformed CHO cell with DNA construct incorporated into chromosomal DNA

Biotechnology companies predictably rebelled at Columbia's demand for future royalties:

> Columbia has obtained its patent protection, reaped very significant rewards, and now the inventions have passed into the public domain. The industry wants Columbia to play by the rules that everybody

70. "The [biotechnology and pharmaceutical] industry understood in 2000 the patents had expired and they would no longer be burdened with that royalty expense in future years." Donald R. Ware, Attorney for Biogen, Genzyme, and Abbott, *quoted in* Agres, *supra* note 30.

71. *See* Biogen Complaint, *supra* note 35, ¶36; Wyeth Complaint, *supra* note 35, ¶23; Serono Complaint, *supra* note 35, ¶40; Marshall, *supra* note 66.

> else plays by, which is you have an invention, you get a patent, and you get one 17-year term [of monopoly rights].[72]

Genentech filed the first lawsuit against Columbia on April 15, 2003, in the Northern District of California;[73] Amgen followed with a similar complaint on June 18, 2003, in the Central District of California.[74] The July 15, 2003 suits lodged by Biogen, Genzyme, and Abbott in the District of Massachusetts attracted widespread press coverage.[75] On August 20, 2003, Wyeth also sued in Massachusetts,[76] as did Baxter Healthcare and Serono near the end of 2003.[77] Each of the eight suits against Columbia advances similar legal theories, including invalidity and unenforceability of the '275 patent, illegal basis for demanding royalties,[78] inequitable conduct in misleading the PTO and patent examiners, inequitable conduct in using both a "submarine patent"[79] strategy and laches for unreasonable delay,[80] breach of good faith and fair dealing,[81] breach of the NIH licensing agreement where Plaintiffs are third-party beneficiaries to that agreement,[82] and violations of 35 U.S.C. §§ 101, 102, 103, and 112.[83] The actions seek declaratory judgment and injunctions. Columbia answered all complaints and offered several affirmative defenses: failure to state a cause of action, failure to plead sufficient particularity, unclean hands, waiver, acquiescence, and ratification of Columbia's conduct.[84]

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72. Donald R. Ware, Attorney for Biogen, Genzyme, and Abbott, *quoted in* Agres, *supra* note 30; *see also Ownership at Too High a Price?*, *supra* note 2, at 953 ("Not surprisingly, the biotechnology industry is not amused.").

73. *See* Genentech Complaint, *supra* note 35; Denise Gellene, *Genentech Sues Columbia over Biotech Patent*, L.A. TIMES., Apr. 18, 2003, at C2.

74. *See* Amgen Complaint, *supra* note 35.

75. *See, e.g.*, Andrew Pollack, *Three More Biotech Firms File Suit Against Columbia Over Patent*, N.Y. TIMES, July 16, 2003, at B2.

76. *See* Wyeth Complaint, *supra* note 35.

77. *See* Baxter Complaint, *supra* note 35; Serono Complaint, *supra* note 35.

78. *See* Genentech Complaint, *supra* note 35, ¶¶ 61, 62.

79. Submarine patents are simply patents that issue after a substantial, possibly intentional delay; submarine patents often correlate with a patentee attempting to exert his patent right over a mature industry. *See* United States Patent and Trademark Office, Questions and Answers Regarding the GATT Uruguay Round and NAFTA Changes to U.S. Patent Law and Practice (Feb. 23, 1995), *at* http://www.uspto.gov/web/offices/com/doc/uruguay/QA.html.

80. *See* Genentech Complaint, *supra* note 35, ¶¶ 4, 37; Biogen Complaint, *supra* note 35, ¶¶ 1, 4, 45; Wyeth Complaint, *supra* note 35, ¶¶ 31–33; Baxter Complaint, *supra* note 35, ¶ 16.

81. *See* Wyeth Complaint, *supra* note 35, ¶¶ 101–03.

82. *See id.* ¶¶ 87, 96.

83. *See* Biogen Complaint, *supra* note 35, ¶¶ 41–42; Wyeth Complaint, *supra* note 35, ¶¶ 25–27.

84. *See* Answer ¶¶ 64–68, Genentech, Inc. v. Tr. of Columbia Univ. (N.D. Cal. 2003) (No. 3:03-cv-01603); Answer to Biogen, *supra* note 67, ¶¶ 77, 81–83; *see also* Agres, *supra*

II. ANALYSIS OF PATENTS-IN-SUIT

A. Comparison of the '216, '665, and '017 Patents with the '275 Patent

As with all patent matters, the analysis of whether the '275 patent is truly different from the '216 patent crucially depends on the claim language.[85] Among the divisional applications arising from the '216 patent, the '665 patent only alters the scope of the claims from the '216 patent by adding express claim language stating that DNA II is "attached to bacterial plasmid or phage DNA."[86] This idea was previously disclosed as a "particularly promising embodiment"[87] in the '216 patent.[88]

The '017 patent only recites five claims, first claiming a CHO cell transformed by integrated DNA I and amplified DNA II. All elements of this claim are contained in claims 54 and 73 of the '216 patent, namely a mammalian cell transformed with incorporated DNA I linked with amplified DNA II. Further, claims 2–4 of the '017 patent exactly correspond with claims 55, 56–61, and 70 of the '216 patent. The only alteration to claims created by the '017 patent is the final claim, expressly claiming a method for producing protein from the particular CHO cell. Although the claims for CHO cells and linked DNA I and DNA II were allowed, the PTO required a terminal disclaimer; therefore these "inventions" could not maintain their patent protection beyond August 16, 2000.

The '275 patent claims a specific CHO cell transformed by a "DNA construct," defined in the patent as DNA I linked to DNA II. The '216 patent must encompass CHO because it quite clearly states "that the process described is generally applicable to all eucaryotic cells . . . though the invention may be most useful in cotransforming mammalian cells."[89] Several other claims of the '275 patent that claim transformed CHO cells are redundant with '216 claims. Therefore the

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note 30 (quoting Robert Kasdin, Senior Executive Vice President at Columbia, "The U.S. patent office has determined that the most recent patent application . . . includes distinct and different inventions. We believe that [the plaintiffs' claims are without merit, that] the U.S. Patent and Trademark Office has come to the correct conclusion, and their conclusion should be respected [by the courts]").

85. *See* 35 U.S.C. § 112 ¶ 2 (2000).

86. U.S. Patent No. 4,634,665 (issued Jan. 6, 1987) claim 1.

87. U.S. Patent No. 4,399,216 (issued Aug. 16, 1983), col. 5, ll. 51–57.

88. In *Ethicon Endo-Surgery, Inc. v. U.S. Surgical Corp.*, the Federal Circuit suggests that embodiments affirmatively disclosed in the specification are quite important in determining the meaning of claims and gives the trial court some latitude in using the specification as an aid to claim interpretation. 149 F.3d 1309, 1318–19, 1320–21 (Fed. Cir. 1996). Thus, the embodiments in the patents are relevant to construing what the '216 patent claims and whether or not subsequent patents claim any larger territory.

89. U.S. Patent No. 4,399,216 (issued Aug. 16, 1983), col. 5, ll. 7–8, 12–14.

inquiry into the similarity of the '216 and '275 patents turns on the definition of "DNA construct." During prosecution, Columbia argued to the PTO examiner that the '216 patent claimed only unlinked DNAs, despite the fact that claim 54 of the '216 patent very clearly recites "a molecule which is formed by linking one of said foreign DNA I molecules to a DNA II molecule corresponding to an amplifiable gene for a dominant selective phenotype not expressed by said eucaryotic cell."[90] To any person of reasonable skill in the art of molecular biology, this description would certainly be considered a "DNA construct," especially in or after 1995 when the '275 patent was prosecuted. Another apparent difference is that the term "glycoprotein" is claimed for the first time in the '275 patent. However, any reasonably skilled artisan would realize that a claim to "proteinaceous material" encompasses proteins that are glycosylated, especially when the '216 patent cites glycoproteins like erythropoietin as examples of proteinaceous material.

The manner in which Columbia chose to prepare the specification for each of the four patents issued over twenty-two years is telling. First, the entire abstract from the '216 patent had three sentences added to it to create the abstract for the '665 patent, which itself was transferred verbatim to the '017 patent, and finally used for the '275 patent with just the introductory sentences removed. Second, each patent has two figures, and the figures are virtually identical for all four patents.[91] Third, and most interesting, is the fact that the written descriptions (including the background of the invention, summary of the invention, and detailed description of the invention) for all four patents are *identical* — save for isolated, minor corrections limited to spelling and grammar.[92] Each of the four written descriptions discusses the same, now antiquated, references and cites research that was ongoing in 1980 as ongoing as of the filing date.[93] These similarities could suggest that the patentee achieved little technological progress in terms of novelty, and possibly that in fact the same subject matter is the focus of both patents.

The differences between the '216 patent and the '275 patent plainly appear to be "more semantic than substantive,"[94] as the '275 patent appears merely to claim a particular embodiment of claims previously disclosed in the '216 patent. Reputable and disinterested

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90. U.S. Patent No. 4,399,216 (issued Aug. 16, 1983) claim 54.

91. The only difference is that drawings for the first three patents were hand-lettered, while the drawings for the '275 patent had typed characters.

92. Redlined comparisons are on file with the Harvard Journal of Law & Technology.

93. For example, both the '216 patent and the '275 patent, cite as "currently underway in the laboratory" a schema for gene isolation using "plasmid rescue," despite a filing date difference of fifteen years. *Compare* U.S. Patent 4,399,216 (issued Aug. 16, 1983), col. 9, ll. 22–27, *with* U.S. Patent No. 6,455,275 (issued Sept. 24, 2002), col. 9, ll. 2–7.

94. Marshall, *supra* note 66.

patent attorneys have commented that the '275 patent "is so similar to what was patented previously in one or more of the three previous patents that [Columbia is] improperly attempting to extend the patent coverage beyond the allowable term . . . . [I]t's the same invention, which is really the issue at hand."[95] As such, the PTO should have required the same terminal disclaimer for the '275 patent as it required for the '665 and '017 patents.

B. Inequitable Prosecution Conduct

The plaintiffs have alleged inequitable conduct in prosecution. Inequitable conduct in prosecution, in the form of either nondisclosure to the PTO or laches, can provide an equitable defense to alleged patent infringement by rendering the patent unenforceable.[96] Proof of inequitable conduct involves establishing by clear and convincing evidence both the "materiality of the nondisclosed or false information" and intent to misrepresent or withhold that information.[97] The materiality test is formulated as: "any information that a reasonable examiner would substantially likely consider important in deciding whether to allow an application to issue as a patent" and need not be limited to prior art.[98] The intent element is satisfied when "the involved conduct, viewed in light of all the evidence, including evidence of good faith, must indicate sufficient culpability to require a finding of intent to deceive . . . . [Evidence of intent] must generally be inferred from the facts and circumstances surrounding the applicant's overall conduct."[99] Determinations of materiality and intent must be based on the underlying facts, and once these thresholds are reached, the trial judge must weigh as a matter of law whether or not inequitable conduct occurred.[100]

Plaintiffs' complaints cite numerous instances of nondisclosure-type inequitable conduct allegedly perpetrated by Columbia as part of the prosecution histories of the various patents, especially the '275 patent. Columbia also allegedly failed to disclose to the PTO examiner the existence of a second co-pending application begun in

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95. Agres, *supra* note 30 (quoting Kathleen M. Williams, who holds a Ph.D. in molecular biology and chairs the patent group of Palmer & Dodge LLP).

96. *See* ROBERT P. MERGES & JOHN F. DUFFY, PATENT LAW AND POLICY: CASES AND MATERIALS 1215–16 (3d ed. 2002).

97. J.P. Stevens & Co. v. Lex Tex Ltd., 747 F.2d 1553, 1559 (Fed. Cir. 1984); Orthopedic Equip. Co. v. All Orthopedic Appliances, Inc., 707 F.2d 1376, 1383 (Fed. Cir. 1983).

98. Akron Polymer Container Corp. v. Exxel Container, Inc., 148 F.3d 1380, 1382 (Fed. Cir. 1998); *see also* MERGES & DUFFY, *supra* note 96, at 1236.

99. Paragon Podiatry Lab., Inc. v. KLM Labs., Inc., 984 F.2d 1182, 1189–90 (Fed. Cir. 1993) (internal citations omitted); *see also* Ulead Systems, Inc. v. Lex Computer & Mgmt. Corp., 351 F.3d 1139, 1146–47 (Fed. Cir. 2003).

100. *See Orthopedic Equip. Co.*, 707 F.2d at 1384; *Lex Tex*, 747 F.2d at 1560.

1995;[101] this information was only disclosed in May 2002, just months before the '275 patent issued.[102] Information from three key scientific papers that had been previously cited by Axel lab members and disclosed in the prosecution history of the '216 patent was omitted from the '275 patent's file history;[103] other relevant prior art Columbia patents were also omitted.[104] The examiner may have been intentionally misled by several false statements offered by Columbia, namely that the '216 patent had never recited a claim for linking DNA I and DNA II, that claims proposed for the '275 had not been previously rejected, and that the '017 patent was not a relevant comparison for obviousness analysis.[105] Each of these misrepresentations individually meets the materiality element because any one of them could have prompted the examiner to find the claims of the '275 patent obvious, and the number of misrepresentations indicates action in a grossly negligent, if not intentional, manner.[106]

The Federal Circuit, in *Symbol Technologies, Inc. v. Lemelson Medical*, recently reaffirmed that "the equitable doctrine of laches may be applied to bar enforcement of patent claims that issued after an unreasonable and unexplained delay in prosecution even though the applicant complied with pertinent statutes and rules."[107] The Federal Circuit construed two Supreme Court precedents that suggested that eight or nine year delays in patent prosecution, respectively, would render the patent unenforceable through laches.[108] Uncontested facts and prosecution history indicate a willful pattern of "submarine patenting" or "evergreening"[109] by Columbia that seems to have been facilitated by selective nondisclosures of prior art to examiners so that the later patents would be found valid. Columbia filed numerous applications with the intent of maintaining a perpetually active prosecution of the Axel patent claims and delaying issuance of actual patents, until an opportune time arose to have the "submarine patent" surface and capture royalties from the latest commercial developments that had utilized the Axel technology.[110] The fifteen year delay from initial filing of the '216 patent to filing of the '275 patent is unreasonable under *Symbol Technologies*. This delay can seemingly only be explained by a motivation to extend its

101. *See* Answer to Biogen, *supra* note 67, ¶ 22.
102. *See* Biogen Complaint, *supra* note 35, ¶ 64; Wyeth Complaint, *supra* note 35, ¶ 52.
103. *See* Genentech Complaint, *supra* note 35, ¶¶ 51–56.
104. *See* Biogen Complaint, *supra* note 35, ¶ 23.
105. *See id*. ¶¶ 48, 51, 53–57; Wyeth Complaint, *supra* note 35, ¶¶ 40–48.
106. *See Lex Tex*, 747 F.2d at 1567; *see also* MERGES & DUFFY, supra note 96, at 1229.
107. 277 F.3d 1361, 1363, 1365, 1368 (Fed. Cir. 2002).
108. *See* Webster Elec. Co. v. Splitdorf Elec. Co., 264 U.S. 463 (1924); Woodbridge v. United States, 263 U.S. 50 (1923).
109. *Columbia's Lesson*, 1 ACUMEN J. OF LIFE SCIS. (Sept.–Oct. 2003), *available at* http://www.acumenjournal.com/issue/v1/3/news10.html.
110. *See* Biogen Complaint, *supra* note 35, ¶ 19.

patent monopoly rights beyond the fixed statutory term. This motivation is consistent with revising all claims to explicitly cover co-transformation using the CHO vector and production of any glycoprotein, processes that cover a substantial portion of the biotechnology industry as it had come to exist. Perhaps by luck, 2002 was an excellent time to "surface" a "submarine patent" in order to cover as many new drugs, and therefore new revenue streams, as possible.[111] The extraordinary length of the delay combined with the breadth of patent coverage make a finding of laches highly probable.

C. Statutory Bar and Obviousness

The plain language of 35 U.S.C. § 102(b) also seems to operate as a bar to the '275 patent. Section 102(b) disallows a patent on any invention that has been patented, described in a printed publication, or publicly sold in the United States more than one year prior to the date of application. To the extent that the '275 patent reclaims material in the '216 patent, the invention has been patented more than one year before application. As far back as 1982 there are publications describing co-transformation of CHO cells.[112] The specific practice of co-transforming CHO cells to produce protein was widely published in standard molecular biology literature from the mid-1980s.[113] Finally, Columbia licensed the invention — in other words publicly sold it — to Genentech in 1987, Serono in 1992, Biogen in 1993, and Genzyme in 1994.[114]

A patent cannot issue if the difference between an invention and the prior art is such that the invention "would have been obvious at the time the invention was made to a person having ordinary skill in the art."[115] Obviousness is a question of law that depends on factual

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111. *See* Section I.B, *supra.*

112. *See* Martin L. Breitman et al., *Introduction and Recovery of a Selectable Bacterial Gene from the Genome of Mammalian Cells*, 2 MOL. CELL. BIOL. 966, 967, 974 (1982); *see also* J.D. Milbrandt et al., *Organization of a Chinese Hamster Ovary Dihydrofolate Reductase Gene Identified by Phenotypic Rescue*, 3 MOL. CELL. BIOL. 1266, 1266, 1272 (1983).

113. *See* Fred A.M. Asselbergs et al., *A Recombinant Chinese Hamster Ovary Cell Line Containing a 300-fold Amplified Tetramer of the Hepatitis B Genome Together with a Double Selection Marker Expresses High Levels of Viral Protein*, 189 J. MOL. BIOL. 401, 402–04, 410–11 (1986); James Ripka et al., *Co-transformation of Lec 1 CHO Cells with N-acetylglucosaminyltransferase 1 Activity and a Selectable Marker*, 42 J. CELL. BIOCHEM. 117, 118, 121, 123 (1990); T. Arakawa et al., *Structure and Activity of Granulocyte Colony-Stimulating Factor Derived from CHO Cells Containing cDNA Coding for Alternatively Spliced Sequences*, 316 ARCH. BIOCHEM. BIOPHYS. 285, 285–87 (1995).

114. "A single offer to sell is enough to bar patentability whether or not the offer is accepted." A.B. Chance Co. v. RTE Corp., 854 F.2d 1307, 1311 (Fed. Cir. 1988).

115. 35 U.S.C. § 103(a) (2000).

inquiries including: (1) the scope and content of the prior art,[116] (2) the level of ordinary skill in the art, (3) the differences between the claimed invention and the prior art, and (4) objective evidence of nonobviousness.[117] Given the '017 patent's claim to a transformed CHO cell, the '216 patent's teaching of using either unlinked or linked DNA I/DNA II, and the '665 patent's teaching of using phage or plasmid DNA, claims regarding the processes of transformation or the actual CHO cells in the '275 patent are obvious. The '216, '665, and '017 patents all arose from a single common invention, were internally cross-referenced, contained identical written descriptions and drawings, and were considered a single patent in light of the terminal disclaimer. The '275 patent contains material copied directly from the earlier patents, merely referring to linked DNA I/DNA II as a "DNA construct" and noting that glycoproteins are a subset of proteinaceous material. Thus, the '275 patent would be obvious over the earlier patents because no inventive step is necessary or inherent in assigning a definition to a concept previously disclosed.

D. Specification Requirements

The fact that all four patents contain identical specifications (except for claims) suggests potential inadequacies in the '275 patent for meeting requirements for written description and enablement.[118] The Federal Circuit has generally held biotechnology inventions to a "higher written description standard than inventions in other areas, such as the mechanical arts."[119] In *Enzo Biochem v. Gen-Probe, Inc.*, the Federal Circuit agreed that Enzo's patent failed to meet the written description requirement because it was only described in functional terms; in other words, the patent "claimed anything that works without defining what works."[120] The PTO promulgated guidelines in 2001 that suggest the written description requirement is met by "disclosure of sufficiently detailed, relevant identifying

116. During prosecution of the '665 patent, Columbia acknowledged that it was obvious in light of the '216 patent, which was a major reason leading to the terminal disclaimer. *See* Biogen Complaint, *supra* note 35, ¶ 17.

117. *See* Graham v. John Deere, Co., 383 U.S. 1, 17–18 (1966).

118. "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art . . . to make and use the same." 35 U.S.C. § 112, ¶ 1 (2000).

119. Jeffie A. Kopczynski, *A New Era for § 112? Exploring Recent Developments in the Written Description Requirement as Applied to Biotechnology Inventions*, 16 HARV. J.L. & TECH. 229, 230 (2002).

120. 285 F.3d 1013, 1018–20 (Fed. Cir. 2002), *vacated by* Enzo Biochem, Inc. v. Gen-Probe, Inc., 323 F.3d 956 (Fed. Cir. 2002). However, "the court did not overturn its prior case law that a 'mere wish or plan' for obtaining an invention is not enough to comply with § 112, ¶ 1." Univ. of Rochester v. G.D. Searle & Co., 249 F. Supp. 2d 216, 223 (W.D.N.Y. 2003).

characteristics."[121] Columbia's first claim in the '275 patent claims all "transformed Chinese hamster ovary cells comprising a DNA construct," but its written description nowhere provides the requisite detail on the new experimentation performed nor a description of the defining or identifying characteristics of these cells. There is thus no proof that Columbia actually possessed or reduced this invention to practice, as everything that works was merely claimed though not satisfactorily described.[122] By statute, the written description must reasonably convey to the person of ordinary skill in the art that the inventor possessed the invention at the filing date.[123]

Enablement is a question of law that asks whether the invention has been described sufficiently such that a skilled artisan would not have to unduly experiment in order to practice the invention.[124] *In re Wands* described eight factors relevant to whether a disclosure is non-enabling; those factors germane to this analysis include (1) quantity of experimentation necessary, (2) amount of guidance presented, and (3) state of prior art.[125] There is an inverse relation between obviousness and enablement based on the state of the prior art. The specification of the '275 patent neither teaches nor guides any more than that of the '216 patent; no additional information was included by Columbia to rescue scientists from undue experimentation.[126] If, however, the state of the prior art, in light of the several scientific publications previously mentioned, was sufficient to allow enablement of the '275 patent, then this patent would simultaneously face a severe obviousness problem.

E. Remedies

As pleadings have not yet been completed in any case against Columbia, discussion of procedural posturing and remedy is wholly speculative. Any motion by plaintiffs for judgment on the pleadings or

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121. Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1 "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (Jan. 5, 2001).

122. *See* Kopczynski, *supra* note 119, at 246–48; *see also* Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1568–69 (Fed. Cir. 1997) (stating that description of a species does not constitute description of the genus of which it is a part).

123. *See* Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563–64 (Fed. Cir. 1991). Columbia would likely have a difficult task of proving that, as of February 25, 1980, the date that the written description effectively was submitted, the inventors fully possessed all technologic expertise ultimately claimed in the '275 patent to sufficiently perform the transformation of CHO with the claimed DNA construct to specifically isolate glycoprotein.

124. *See* Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1365 (Fed. Cir. 1997).

125. 858 F.2d 731, 737 (Fed. Cir. 1988).

126. *Cf.* Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1209–10 (Fed. Cir. 1991) (stating that where there are many possibilities for making the claimed invention and the inventor has only disclosed a few, the patent grant will be limited accordingly).

summary judgment will likely fail in light of material factual disputes underlying Columbia's conduct and the validity of the '275 patent.[127]

Plaintiffs have all requested awards of costs under 35 U.S.C. § 285, which allows the court to award reasonable fees in "exceptional cases."[128] The award of such fees does not become an issue until the litigation has been completed, however.[129] Conduct "short of fraud" can render the case "exceptional," though such a determination must turn on analysis of five factors: (1) good faith of losing party, (2) expense caused by misconduct, (3) materiality of misconduct, (4) commonness of practice, and (5) misconduct of prevailing party.[130] Based on the pleadings from the eight cases, plaintiffs seem to have a legitimate chance of having this litigation declared an exceptional case. Columbia has allegedly acted in bad faith with its "submarine patenting" strategy and in misleading a PTO examiner; the Federal Circuit has determined that that extent of misrepresentation can be material.[131]

While trial of the patent case could span years, the alternative procedural mechanism of patent re-examination may lead to an expedited resolution.[132] Any person may petition the PTO for an ex parte review of any claim or patent based on a prior art reference submitted to the PTO.[133] On February 26, 2004, the Public Patent Foundation filed a request for re-examination, motivated in part by concerns that the '275 patent "harm[s] the public health because consumers will be forced to pay higher prices in order to compensate the [biotechnology and pharmaceutical companies] for the royalties" owed to Columbia University.[134] The Director of the PTO now has three months — until May 26, 2004 — to "determine whether a substantial new question of patentability" has arisen.[135] A final remedy available to the PTO is the possibility of sanctioning Columbia's attorneys practicing before the PTO.[136]

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127. *See* FED. R. CIV. P. 12(c), 56.

128. Blonder-Tongue Labs., Inc. v. Univ. of Ill. Found., 402 U.S. 313, 347 (1971).

129. *See id*.

130. *See* Martin M. Heit, *Allegation of Misconduct in Prosecution of Patent Application as Rendering Subsequent Patent Action an "Exceptional Case" for Purposes of 35 U.S.C. § 285*, 62 A.L.R. FED. 733, §§ 4, 5 (1983).

131. *See, e.g.*, J.P. Stevens & Co. v. Lex Tex Ltd., 747 F.2d 1553 (Fed. Cir. 1984).

132. *See* 35 U.S.C. §§ 301–07 (2000).

133. *See id*. §§ 301, 302.

134. Press Release, Public Patent Found., PUBPAT Asks Patent Office to Revoke Cotransformation Patent to Save Public Hundreds of Millions of Dollars (Feb. 26, 2004), *at* http://www.pubpat.org/Axel_Reexam.htm.

135. 35 U.S.C. § 303 (2000).

136. *See, e.g.*, Edwin S. Flores & Sanford E. Warren, *Inequitable Conduct, Fraud, and Your License to Practice Before the United States Patent and Trademark Office*, 8 TEX. INTELL. PROP. L.J. 299, 314–15 (1999) (discussing the Committee on Discipline and levels of sanction applicable to practitioners).

III. THE UNIVERSITY TRANSFORMED BY THE PROFIT GENE: BROADER POLICY ISSUES RAISED BY THE AXEL PATENT LITIGATION

A. University Commercialization

One of the most common arguments offered against the policy of university commercialization is that taxpayers are paying twice to fund research — once with tax dollars to subsidize research and a second time through "skyrocketing costs" of drugs.[137] One way to conceptualize the role of university commercialization is to compare its economic impact before and after passage of the Bayh-Dole Act. Studies have shown that for every dollar of government-sponsored research, up to $10,000 is required to fully develop, commercialize, and realize a useful product.[138] The Bayh-Dole Act was designed to induce private entities — like universities — to fund these large, risky undertakings.[139] Prior to 1980, universities annually secured about 250–300 patents and approximately 5% of those were commercialized.[140] Pat Harsche, President of the Association of University Technology Managers, notes that a "lot of technology sat on the shelf before universities began to really apply for patents."[141] As a result of the Bayh-Dole Act, during the last twenty years, the entrepreneurial incentive has been unleashed to empower universities, professors, and graduate students. During this span, there has been a tenfold increase in university patent output (3,272 patents in the year 2000); 2,400 spinoff firms created, of which nearly three quarters remain viable; creation of hundreds of thousands of jobs; and an annual GDP impact estimated to be in the $40–$50 billion range.[142] Analyses of university commercialization show that universities in Germany, France, and other nations lagged behind the scientific and

137. Peter Arno & Michael Davis, *Paying Twice for the Same Drugs*, WASH. POST, Mar. 27, 2002, at A21; *see also* Elias, *supra* note 53 (quoting Michael Davis, Professor of Intellectual Property Law, Cleveland State University: "It's an embarrassment. The government paid for all of the research and development. Taxpayers are essentially paying twice.").

138. *See Innovation's Golden Goose*, *supra* note 29; Birch Bayh & Bob Dole, *Our Law Helps Patients Get New Drugs Sooner*, WASH. POST, Apr. 11, 2002, at A28.

139. *See* Bayh & Dole, *supra* note 138.

140. *See* Arti K. Rai & Rebecca S. Eisenberg, *Bayh-Dole Reform and the Progress of Biomedicine*, 91 AM. SCIENTIST 52, 53 (2003).

141. *Innovation's Golden Goose*, *supra* note 29; Elias, *supra* note 53.

142. *See* Robert Kneller, *Technology Transfer: A Review for Biomedical Researchers*, 7 CLIN. CANCER RES. 761, 762 (2001); *Innovation's Golden Goose*, *supra* note 29; Elias, *supra* note 53; ASS'N OF AM. UNIVS., UNIVERSITY TECHNOLOGY TRANSFER OF GOVERNMENT-FUNDED RESEARCH HAS WIDE PUBLIC BENEFITS (1998), *available at* http://www.aau.edu/research/TechTrans6.3.98.html.

entrepreneurial output of United States universities operating under Bayh-Dole.[143]

Many dispute these possible economic dividends and attack the basic premise of the Bayh-Dole Act. Numerous inventions would undoubtedly be commercialized without the supplemental patent incentive. The Bayh-Dole Act lacks distinct regulation for "inventions that lead directly to commercial products and fundamental advances that enable further scientific studies."[144] Many commentators hypothesize about a potential long-term inhibitory effect on diverse facets of applied biological research by restricting dissemination of technology.[145] The Axel patents have been cited as the prototypical example of a fundamental advance and not a commercial product, from which society would realize more benefits from widespread dissemination and exploitation rather than restriction via licensing.[146] Another prominent example is Harvard University's OncoMouse, which is protected by broad intellectual property claims. Many oncologists and researchers feel that this broad protection verges on monopolization of "animals[,] . . . genes, and other biological functions," that it "overly restricts their work," and creates an "obstacle" to translating research from the bench to the bedside.[147] While some "fundamental advances" will require patent protection in order to stimulate commercialization and thereby maximize social welfare, others, like the technique of co-transformation, may generate increased societal utility as the technology is licensed more broadly and moves to the public domain in an equitable amount of time.[148] For both co-transformation technology and the OncoMouse, the breadth of the patent claims is inextricably intertwined with the issue of balancing the patentee's rights versus promoting scientific and medical progress.[149] Thus, the challenge for future legislation and regulation will be to recalibrate the Bayh-Dole framework and patent requirements for biotechnology to achieve this delicate balance.

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143. *See* Shreefal Mehta, *The Emerging Role of Academia in Commercializing Innovation*, 22 NATURE BIOTECH. 21, 21 (2004).

144. Rai & Eisenberg, *supra* note 140, at 52.

145. *See id*. at 52–54.

146. *See id*. at 52.

147. Paul Elias, *Cancer Researchers Frustrated by Patent on Modified Mouse*, HELENA INDEP. REC. (Nov. 2, 2003), *available at* http://www.helenair.com/articles/2003/11/02/national/c09110203_02.txt; *see also* Rai & Eisenberg, *supra* note 140, at 55–56.

148. *See* Rai & Eisenberg, *supra* note 140, at 56–57 (citing the example of DNA sequencing machines as a "fundamental advance" which required patent protection in order to become adequately commercialized).

149. *See Ownership at Too High a Price?*, *supra* note 2, at 953; *see generally* Kopczynski, *supra* note 119.

Universities operating under the current Bayh-Dole framework "have become much more sophisticated and business-like."[150] In recent years, universities have faced budget shortfalls and dwindling government funding as they seek to fund ever-expanding research initiatives. Technology transfer revenue may be viewed by some universities as a means to supplement research expenditures, if not an outright attempt to turn research into profit.[151] Concomitant with increased fiscal and business-like motivations, the ideal of free academic exchange has mutated to include more aspects of competition and secrecy.[152] For example, "[e]xchanges of DNA sequences, laboratory animals, reagents and data that were once shared freely are today subject to licenses, material-transfer and database-access agreements. These arrangements have to be reviewed, and may have to be negotiated before research may proceed."[153] Universities have clearly become more inclined to aggressively protect all types of intellectual property, to the point of now employing adversarial techniques and litigation though such practices used to be rare.[154]

Institutions are struggling to retain their focus on the public mission of research as part of a more balanced approach to university commercialization. For example, MIT's Technology Licensing Office Director Lita Nelson rejects the view that the primary purpose of licensing is for financial gain to the university, stating "[w]e're in it to get the technology developed and to make a little money on the side."[155] Though the Columbia case has attracted national attention, it is not likely a harbinger of a systemic problem with university commercialization. Joyce Brinton, who serves as Director of the Office of Technology Transfer at Harvard University, comments that because the case is exceedingly unique and dependent on a host of specific facts (especially with respect to its particular patents and the filing of patent applications immediately before June 8, 1995), the particular issue of continuation patents in a similar university commercialization context is not likely to reoccur.[156] The only other

150. Elias, *supra* note 53 (quoting Dr. Robert Cook-Deegan, head of Duke University's Center for Genome Ethics, Law, and Policy).

151. *See, e.g.*, *Ownership at Too High a Price?*, *supra* note 2, at 953. However, technology transfer royalties — in the aggregate and by institution — represent only a fraction of total university research expenditures. *See* Howard, *supra* note 34, at 955 (noting in 2001 American and Canadian research institutions spent over $30 billion on research while earning just over $1 billion in royalties); *see also supra* note 53 and accompanying text.

152. *See* Rai & Eisenberg, *supra* note 140, at 52; *see also* Elias, *supra* note 147.

153. Rai & Eisenberg, *supra* note 140, at 55.

154. *See* Howard, *supra* note 34, at 956.

155. Agres, *supra* note 49.

156. Telephone interview with Joyce Brinton, Director, Office for Technology and Trademark Licensing, Harvard University (Feb. 18, 2004).

similar case involves the licensing of platinum anti-cancer compounds by Michigan State University. In that instance, the first patent on the compounds issued in 1979 and should have expired in 1996[157]; however, an application filed before June 8, 1995 resulted in a 1996 patent, thus prolonging patent protection until 2013.[158] As a result, university administrators have generally not felt a need to examine or revise their technology transfer policies or practices. It is unclear how many applications from before June 8, 1995, remain pending in the PTO. Depending on this number and the PTO's treatment of such applications, the same issue surrounding extension of the Axel patents might reoccur. However, Columbia may have "yet another patent application pending at the Patent Office for the same co-transformation technology,"[159] so the controversy over university commercialization may not end with the present set of lawsuits.

B. Seeking Individual Exemptions to Patent Law via Congress

Had the efforts of Columbia and Senator Gregg been successful, a dangerous precedent would have been established that would have undermined the patent system and the primacy of the PTO. By creating a pretext for special treatment by selective Congressional intervention, it would be possible that manufacturers of many blockbluster pharmaceuticals, such as Claritin,[160] could have successfully petitioned Congress to extend their patents.[161]

The patent system can only be administered efficiently if every invention is allotted one fixed period during which it can be monopolized by its inventor. That duration should be set by Congress such that there is a reasonable balance of short-term public interest (in terms of cheaper products) versus the incentive to invest (and long-

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157. *See* U.S. Patent No. 4,177,263 (issued Dec. 4, 1979).

158. *See* Eisenstein & Resnick, *supra* note 47, at 881–82; *see also* U.S. Patent No. 5,562,925 (issued Oct. 8, 1996).

159. Public Patent Found., *supra* note 134; Answer to Biogen, *supra* note 67, ¶22 ("Columbia admits and alleges that on June 7, 1995, it filed United States Application . . . 08/477,159 (the "'159 Application") . . . . [T]he '159 Application is still pending [at least as of Sept. 5, 2003]."); *see also supra* note 101 and accompanying text.

160. With the Claritin patent due to expire in 2002, Schering-Plough in 1996 began a massive program of congressional lobbying to extend it. *See* Public Citizen, *Schering-Plough Plows Ahead with High-Priced Lobbying Campaign for a Claritin Patent Extension*, *available at* http://www.citizen.org/congress/reform/archives/claritin/articles.cfm?ID=1074 (last modified Sept. 30, 1999). The lobbying effort was ultimately unsuccessful. *See* Bloomberg News, *Schering-Plough to Produce Five New Drugs in Singapore Plant*, BLOOMBERG.COM (Mar. 26, 2004), *at* http://quote.bloomberg.com/apps/news?pid=10000080&sid=a0btUHiU972E&refer=asia.

161. *See* Bureau of National Affairs, *supra* note 65, at A-41; *Columbia's Drug Patent Gift*, WIRED NEWS (May 18, 2000), *available at* http://www.wired.com/news/technology/0,1282,36444,00.html; *Stopping the Patent Clock*, WASH. POST, June 26, 2000, at A18.

term public interest in having a greater diversity and higher quality of products). Columbia's argument that it was deprived of significant royalty for the first five years of the '216 patent due to delays in FDA drug review[162] is not persuasive. The purposes of Hatch-Waxman would not be served by extending patent duration for inventions further up the development stream from the drugs themselves. Basic research tools earn licensing fees long prior to FDA approval of any completed pharmaceutical product, and do not directly translate into one particular product, so multiple revenue streams are available. Additionally, a licensing university receives guaranteed revenue streams risk-free while shifting all risks to the licensor.

Even if it had been proper for Columbia to seek congressional intervention in mid-2000, the manner in which the process was undertaken seems underhanded and in direct contravention of promoting political discourse on an important issue. By burying the special provision for Columbia in an appropriations bill, the congressional committee process was eviscerated, as no hearings or discussions were able to be held on the particular patent issue.[163]

C. Conclusion

The short-term outcome of the Columbia Axel patent litigations will probably be multiple similar judgments that the '275 patent is unenforceable, invalid, or both. Under the "exceptional case" statute, it seems at least possible that Columbia could be liable for the attorneys' fees of many of its current adversaries.

Regardless of outcome, over the long term, this case will come to be publicly associated with the significant policy issues that occur at the interface of government, academia, and industry. Since the signing of the Constitution, the U.S. patent system has played a role in commercialization by protecting core intellectual property and

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162. *See* Rovner, *supra* note 64; *Columbia's Drug Patent Gift*, *supra* note 161.

163. Many other Senators rightly called for a correction of the procedural and substantive injustice that this amendment could cause.

> These proposed items should not be slipped into any Appropriations bills. They have not had appropriate congressional review and Congress has not had an opportunity to review their merits individually . . . . These riders should see the light of day before being added in conference to a bill that had no such provisions as passed by the House and Senate.

Letter from Senators Richard Durbin, Patrick Leahy, John Edwards, James Jeffords, Tim Johnson, Ted Kennedy, Olympia Snowe, and Paul Wellstone to Senators Ted Stevens, Chair, Appropriations Committee, and Conrad Burns, Chair, Military Construction Appropriations Subcommittee, *quoted in* Bureau of National Affairs, *supra* note 65, at A-41. Additionally, Gregg's interpretation of the Hatch-Waxman Act was considered frivolous by many, including the Act's sponsor Representative Henry Waxman, who commented on it as "another fly-by-night patent extension." *Columbia's Drug Patent Gift*, *supra* note 161; *see also supra* note 63.

stimulating novel inventions. Recent changes in federal law have enhanced universities' ability to participate in the entire process from idea to product, and there is significant evidence that this practice has generated substantial economic and social benefit. Nevertheless, the public will question why Columbia University would adopt a systematic program of "submarine patenting," mislead PTO officials, and mount a congressional campaign to gain an individualized patent extension. Under a framework with enhanced economic incentives, the profit gene has modified university behavior to mimic similarly situated, but purely profit driven, enterprises like pharmaceutical and biotechnology companies. Whereas pecuniary motivations and concerns were once taboo in academia,[164] it is now common for research scientists and physicians to hold professorial appointments and affiliations with private ventures simultaneously.[165] This case will serve to stimulate further consideration — by both universities and policymakers — of the changing roles of the university, interpretation of patent laws and practice before the PTO, and whether there are ethical limits on university commercialization.

164. *See, e.g.*, Mehta, *supra* note 143, at 22.

165. One example is Professor Eric S. Lander at MIT, who co-founded Millennium Pharmaceuticals. Professor Lander remains on the Board of Directors at Millenium Pharmaceuticals, while also serving as Director of MIT's Broad Institute. *See* Millennium Pharmaceuticals, *Board of Directors Bios*, *available at* http://www.mlnm.com/media/bios/index.asp#brd (last visited Mar. 8, 2004).

APPENDIX: PROTEIN-BASED DRUGS PRODUCED IN EUKARYOTIC VECTORS BASED ON AXEL PATENT TECHNOLOGY[166]

Generic Name (Brand Name, Manufacturer, FDA Approval Date)

Adalimumab (Humira, Abbott, Dec. 31, 2002): "a recombinant human IgG1 monoclonal antibody . . . produced by recombinant DNA technology in a mammalian cell [Chinese hamster ovary]."[167]

Agalsidase beta (Fabrazyme, Genzyme, Apr. 24, 2003): a glycosylated "recombinant human alpha-galactosidase A . . . produced by recombinant DNA technology in a Chinese Hamster Ovary mammalian cell expression system."[168]

Alefacept (Amevive, Biogen Idec, Jan. 30, 2003): an "immunosuppressive dimeric fusion protein" consisting of an anti-CD2 domain linked to human IgG1 "produced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) mammalian cell expression system."[169]

Alteplase (Activase and Cathflo Activase, Genentech, Nov. 13, 1987, and Sept. 4, 2001): "a tissue plasminogen activator produced by recombinant DNA technology . . . by an established mammalian cell line (Chinese Hamster Ovary cells [in nutrient medium containing

166. This list is comprised of products that are (1) made by companies who are parties to the various Columbia suits; (2) have been approved by April 1, 2004; (3) are used in clinical practice; and (4) have an approved "United States Prescribing Information" document or package insert available. It is likely that other protein-based drugs are based on the Axel patent. For example, Corixa's tositumomab (Bexxar) is a recently approved radioimmunotherapeutic monoclonal antibody that is also cultured from a mammalian cell, and Ilex's alemtuzumab (Campath) is a monoclonal antibody produced in CHO cells in neomycin culture. *See* Corixa Corp., Bexxar (tositumomab and iodine I 131 tositumomab) U.S. Prescribing Information, *available at* http://www.corixa.com/Bexxar/BexxarPackageInsert.pdf (last visited Mar. 10, 2004); Ilex Oncology, Inc., Campath (alemtuzumab) U.S. Prescribing Information, *available at* http://www.campath.com/pi.html (last visited Mar. 10, 2004). These and other drugs are not included on the list or in the analysis solely because the companies that manufacture or market these drugs are not parties to the suits mentioned *supra*.

167. Abbott Labs., Humira (adalimumab) U.S. Prescribing Information, *available at* http://www.rxabbott.com/pdf/humira.pdf (last visited Mar. 26, 2004); Euro. Agency for the Evaluation of Medicinal Prods., Summary of Product Characteristics: Humira (Sept. 8, 2003), *available at* http://www.emea.eu.int/humandocs/PDFs/EPAR/humira/400803en4.pdf.

168. Genzyme Corp., Fabrazyme (agalsidase beta) U.S. Prescribing Information (Apr. 24, 2003), *available at* http://www.genzyme.com/corp/Fabrazyme_PI_final.pdf.

169. Biogen Idec, Amevive (alefacept) U.S. Prescribing Information (Feb. 2003), *available at* http://www.amevive.com/amevive_web/web_content/en_US/forms/AMEVIVE_Label_I63007_1.pdf.

the antibiotic gentamicin]) into which the cDNA for alteplase has been genetically inserted."[170]

Bevacizumab (Avastin, Genentech, Feb. 26, 2004): "a recombinant humanized monoclonal IgG1 antibody that . . . is produced in a Chinese Hamster Ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin."[171]

Choriogonadotropin alfa (Ovidrel, Serono, Sept. 20, 2000): "recombinant human Chorionic Gonadotropin, r-hCG" produced in "genetically modified Chinese Hamster Ovary (CHO) cells from an extensively characterized cell bank."[172]

Darbepoetin alfa (Aranesp, Amgen, Sept. 17, 2001): a glycosylated recombinant human erythropoietin derivative produced in Chinese hamster ovary cells.[173]

Dornase alfa (Pulmozyme, Genentech, Dec. 30, 1993): "recombinant human deoxyribonuclease I (rhDNase) . . . produced by genetically engineered Chinese Hamster Ovary (CHO) cells containing DNA encoding for the native human protein . . . carried out in a nutrient medium containing the antibiotic gentamicin."[174]

Efalizumab (Raptiva, Genentech, Oct. 27, 2003): "an immunosuppressive recombinant humanized IgG1 kappa isotype monoclonal antibody . . . produced in a Chinese hamster ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin."[175]

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170. Genentech, Inc., Activase (alteplase) U.S. Prescribing Information, *available at* http://www.gene.com/gene/products/information/cardiovascular/activase/index.jsp (last visited Mar. 26, 2004); Genentech, Cathflo Activase (alteplase) U.S. Prescribing Information, *available at* http://www.gene.com/gene/products/information/cardiovascular/cathflo-activase/insert.jsp (last visited Mar. 26, 2004).

171. Genentech, Inc., Avastin (bevacizumab) U.S. Prescribing Information, *available at* http://www.gene.com/gene/products/information/pdf/avastin-prescribing.pdf (last visited Mar. 26, 2004).

172. Serono, Inc., Ovidrel (choriogonadotropin alfa) U.S. Prescribing Information, *available at* http://www.seronofertility.com/pdfs/OvidrelPFS_package_insert_10-03.pdf (last visited Mar. 26, 2004).

173. *See* Amgen, Inc., Aranesp (darbepoetin alfa) U.S. Prescribing Information (Dec. 17, 2002), *available at* http://www.aranesp.com/pdf/aranesp_PI.pdf.

174. Genentech, Inc., Pulmozyme (dornase alfa) U.S. Prescribing Information (Jan. 2001), *available at* http://www.gene.com/gene/products/information/opportunistic/pulmozyme/insert.jsp.

175. Genentech, Inc., Raptiva (efalizumab) U.S. Prescribing Information, *available at* http://www.gene.com/gene/products/information/immunological/raptiva/insert.jsp (last visited Mar. 26, 2004).

Epoetin alfa (Epogen, Amgen, Jun. 1, 1989; Procrit, Johnson & Johnson, Dec. 31, 1990): a "glycoprotein manufactured by recombinant DNA technology . . . [and] produced by mammalian cells [Chinese hamster ovary] into which the human erythropoietin gene has been introduced."[176]

Etanercept (Enbrel, Immunex, now Amgen, Nov. 2, 1998): a TNF antagonist that is a glycosylated, dimeric, fusion protein of the TNF receptor and the Fc portion of an IgG antibody produced in a Chinese hamster ovary cell from a recombinant DNA construct.[177]

Factor VIII (Advate, Baxter, July 25, 2003): an albumin-free "purified glycoprotein . . . synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line."[178]

Factor VIII (Recombinate, Baxter, Dec. 10, 1992): a "glycoprotein synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line."[179]

Factor VIII (ReFacto, Wyeth, Mar. 6, 2000): purified factor VIII "produced by recombinant DNA technology" in "a genetically engineered Chinese hamster ovary (CHO) cell line."[180]

Factor IX (BeneFix, Wyeth, Feb. 12, 1997): purified factor IX "produced by recombinant DNA technology" in "a genetically engineered Chinese hamster ovary (CHO) cell line."[181]

Follitropin alfa (Gonal-f, Serono, Sept. 29, 1997): human follicle stimulating hormone "of recombinant DNA origin" produced in "genetically modified Chinese Hamster Ovary (CHO) cells."[182]

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176. Amgen, Inc., Epogen (epoetin alfa) U.S. Prescribing Information (Oct. 18, 2002), *available at* http://www.amgen.com/product/epogen.PI.pdf; Ortho Biotech Prods., L.P., Procrit (epoetin alfa) U.S. Prescribing Information (Nov. 2002), *available at* http://healthcareprofessionals.orthobiotech.com/products/procrit/procrit.pdf.

177. *See* Wyeth Labs., Enbrel (etanercept) U.S. Prescribing Information (Oct. 17, 2003), *available at* http://www.wyeth.com/content/ShowLabeling.asp?id=101.

178. Baxter HealthCare Corp., Advate (factor VIII) U.S. Prescribing Information, *available at* http://www.advate.com/images/pdf/prescribing_info_english.pdf (last visited Mar. 26, 2004).

179. Baxter HealthCare Corp., Recombinate (factor VIII) U.S. Prescribing Information, *available at* http://www.advate.com/images/pdf/prescribing_info_english.pdf (last visited Mar. 26, 2004).

180. Wyeth Pharm. Inc., ReFacto (factor VIII) U.S. Prescribing Information, *available at* http://www.wyeth.com/content/ShowLabeling.asp?id=140 (last visited Mar. 26, 2004).

181. Wyeth Pharm. Inc., BeneFix (factor IX) U.S. Prescribing Information, *available at* http://www.wyeth.com/content/ShowLabeling.asp?id=92 (last visited Mar. 26, 2004).

182. *See* Serono, Inc., Gonal-f (follitropin alfa) U.S. Prescribing Information, *available at* http://www.seronofertility.com/pdfs/Gonal-f_PI.pdf (last visited Mar. 26, 2004).

Ibritumomab Tiuxetan (Zevalin, Biogen Idec, Feb. 19, 2002): a monoclonal antibody produced in Chinese hamster ovary cells conjugated with tiuxetan chelator.[183]

Imiglucerase (Cerezyme, Genzyme, May 23, 1994): "an analogue of the human enzyme, beta-glucocerebrosidase, produced by recombinant DNA technology . . . using mammalian cell culture (Chinese Hamster Ovary)."[184]

Interferon beta-1a (Avonex, Biogen Idec, May 17, 1996): glycosylated interferon beta-1a "produced by recombinant DNA technology using genetically engineered Chinese Hamster Ovary cells into which the human interferon beta gene has been introduced."[185]

Interferon beta-1a (Rebif, Serono, Mar. 7, 2002): glycosylated interferon beta-1a "produced by recombinant DNA technology using genetically engineered Chinese Hamster Ovary cells into which the human interferon beta gene has been introduced."[186]

Laronidase (Aldurazyme, Genzyme, Apr. 30, 2003): a "polymorphic variant of the human enzyme, alpha-L-iduronidase that is produced by recombinant DNA technology in a Chinese hamster ovary cell line."[187]

Omalizumab (Xolair, Genentech, June 20, 2003): "a recombinant DNA-derived humanized IgG1κ monoclonal antibody . . . produced by a Chinese hamster ovary cell suspension culture in a nutrient medium containing the antibiotic gentamicin."[188]

Rituximab (Rituxan, Genentech, Nov. 26, 1997): a "genetically engineered chimeric murine/human monoclonal antibody . . .

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183. Biogen Idec, Zevalin (ibritumomab tiuxetan) U.S. Prescribing Information, *available at* http://www.zevalin.com/pdf/zevalin_pi.pdf (last visited Mar. 26, 2004).

184. Genzyme Corp., Cerezyme (imiglucerase) U.S. Prescribing Information, *available at* http://www.cerezyme.com/global/pi.pdf (last visited Mar. 26 2004).

185. Biogen Idec, Avonex (interferon beta-1a) U.S. Prescribing Information, *available at* http://www.avonex.com/forms/Avonex_Lyo_PI.pdf (last visited Mar. 26, 2004).

186. Serono, Inc., Rebif (interferon beta-1a) U.S. Prescribing Information, *available at* http://www.mslifelines.com/Rebif_PI.pdf (last visited Mar. 26, 2004).

187. Genzyme Corp., Aldurazyme (laronidase) U.S. Prescribing Information, *available at* http://www.aldurazyme.com/pdf/az_us_hc_pi.pdf (last visited Mar. 26, 2004).

188. Genentech, Inc., Xolair (omalizumab) U.S. Prescribing Information, *available at* http://www.gene.com/gene/products/information/immunological/xolair/insert.jsp (last visited Mar. 26, 2004).

produced by a mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin."[189]

Somatropin (Serostim, Serono, Aug. 23, 1996): recombinant human growth hormone "produced by a mammalian cell line (mouse C127) that has been modified by the addition of the hGH gene."[190]

Tenecteplase (TNKase, Genentech, June 2, 2000): "a tissue plasminogen activator (tPA) produced by recombinant DNA technology using an established mammalian cell line (Chinese Hamster Ovary cells) . . . . Cell culture is carried out in nutrient medium containing the antibiotic gentamicin."[191]

Thyrotropin alfa (Thyrogen, Genzyme, Nov. 30, 1998): a "highly purified recombinant form of human thyroid stimulating hormone (TSH), a glycoprotein which is produced by recombinant DNA technology. . . . in a genetically modified Chinese hamster ovary cell line."[192]

Trastuzumab (Herceptin, Genentech, Sept. 25, 1998): "a recombinant DNA derived humanized monoclonal antibody . . . produced by a mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin."[193]

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189. Genentech, Inc., Rituxan (rituximab) U.S. Prescribing Information, *available at* http://www.gene.com/gene/products/information/oncology/rituxan/insert.jsp (last visited Mar. 26, 2004).

190. Serono, Inc., Serostim (somatotropin) U.S. Prescribing Information, *available at* http://www.aidswasting.com/aids/serostim/images/serostim_pi.pdf (last visited Mar. 26, 2004).

191. Genentech, Inc., TNKase (tenecteplase) U.S. Prescribing Information, *available at* http://www.gene.com/gene/products/information/cardiovascular/tnkase/insert.jsp (last visited Mar. 26, 2004).

192. Genzyme Corp., Thyrogen (thyrotropin alfa) U.S. Prescribing Information, *available at* http://www.thyrogen.com/global/pi.pdf (last visited Mar. 26, 2004).

193. Genentech, Inc., Herceptin (trastuzumab) U.S. Prescribing Information, *available at* http://www.gene.com/gene/products/information/oncology/herceptin/insert.jsp (last visited Mar. 26, 2004).