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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).

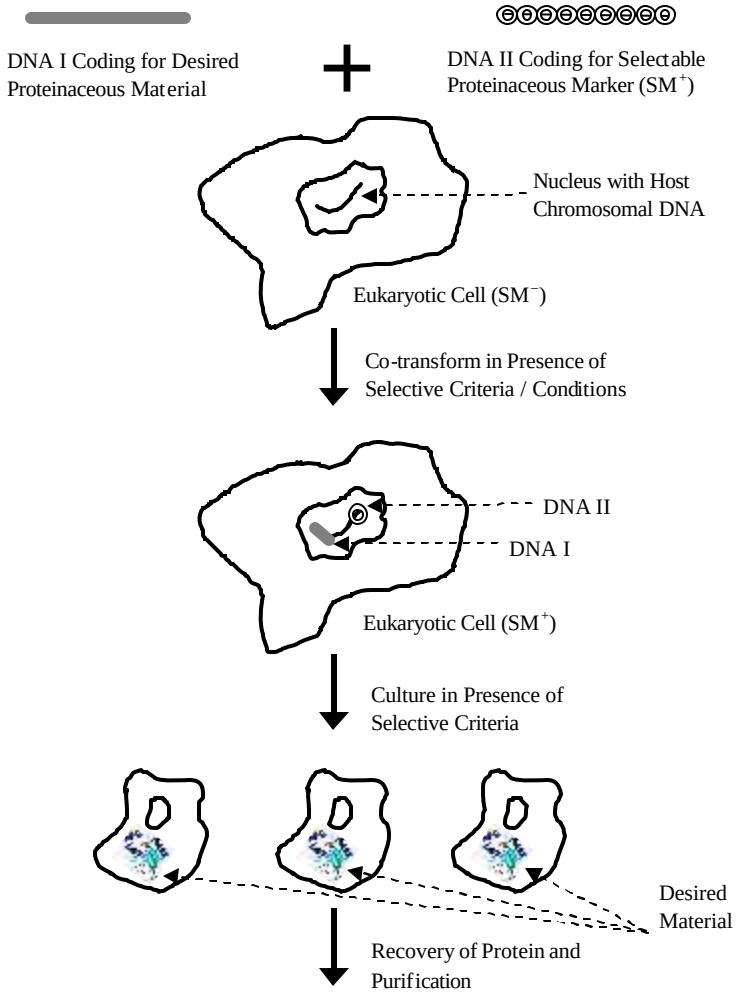
genotype with two different foreign DNA molecules.[11] One DNA molecule (hereinafter "DNA I") would be the gene coding for the desired proteinaceous material, and the other DNA molecule (hereinafter "DNA II") would be a gene for a selectable marker. A selectable marker is a particular gene that provides 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]

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).

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