United States District Court,
D. Massachusetts.

The TRUSTEES OF COLUMBIA UNIVERSITY IN the CITY OF NEW YORK,
Plaintiff.
v.
ROCHE DIAGNOSTICS GMBH, formerly known as Boehringer Mannheim GmbH,
Defendant.

No. 93-11512-NG

Dec. 11, 2000.

Owner of genetic engineering patents sued competitor for infringement. Construing the claims, the District Court, Gertner, J., held that: (1) eucaryotic host cells discussed in linked cotransformation claims included both wild-type and mutant cells, and (2) product by process claims were not limited to products prepared by processes set forth in claims.

Ordered accordingly.

4,399,216, 4,634,665, 5,179,017. Construed.

Sarah C. Columbia, Choate, Hall & Stewart, Boston, MA, Rodney E. Gould, Rubin, Hay & Gould, Framingham, MA, Donna A. Tobin, Cooper & Dunham LLP, New York, NY, Boston, MA, for plaintiff.

Peter F. Felfe, Fulbright & Jaworski, New York, NY, Cornelius J. Moynihan, Jr., Nicholas G. Papastavros, Nixon Peabody, Boston, MA, for GmbH Boehringer Mannheim.

MEMORANDUM AND ORDER RE: MARKMAN CLAIM CONSTRUCTION

GERTNER**, District Judge.**

The plaintiff, The Trustees of Columbia University in the City of New York ("Columbia"), and the defendant, Roche Diagnostics GmbH ("Roche"), have submitted pleadings in support of their respective interpretations of the claims of the patents at issue [docket entries # 228, # 234, # 236]. The Court also conducted a Markman hearing FN1 on June 2, 2000, at which the Court heard testimony from Columbia's expert, Dr. Robert A. Weinberg ("Weinberg") FN2 and Roche's expert, Dr. Andrew C. Webb ("Webb"). FN3

FN1. The term "Markman hearing" stems from the decision in Markman v. Westview Instruments, Inc., 52 F.3d 967 (Fed.Cir.1995), *aff'd* 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996).

FN2. Weinberg is the Daniel K. Ludwig Professor of Cancer Research at the Massachusetts Institute of Technology.

FN3. Webb is a professor of biological sciences at Wellesley College who teaches undergraduate courses in cellular biology, genetics, and molecular biology.

Based on all of the record before me, I find that the claims of these patents are as described below.

I. *FACTS*

A. *Introduction*

The patents at issue are collectively referred to as the "Axel patents," named after one of the inventors, Dr. Richard Axel. They are U.S.Patent No. 4,399,216 ("the '216 patent"), U.S.Patent No. 4,634,665 ("the '665 patent"), and U.S.Patent No. 5,179,017 ("the '017 patent"). The patents are directed at processes commonly referred to as "genetic engineering." They detail methods of altering the genetic composition, i.e. genotype or genome, of eucaryotic cells FN4 so that they may produce substances valued for therapeutic and/or commercial reasons. The technology provides a way to insert DNA FN5 (genes that code for products of interest) into the genetic make-up of a recipient cell ("host cell") enabling that cell to create the desired product for harvesting.

FN4. Eucaryotic cells are cells that have a defined nucleus. They make up organisms classified under the Superkingdom Eucaryotes, including organisms of the Plant and Animal Kingdoms. The ability to alter the genetic make-up of eucaryotic cells, as opposed to procaryotic cells (cells that make up bacteria and lack a defined nucleus), represented a significant advance over previous genetic engineering techniques.

FN5. DNA is deoxyribonucleic acid. It is an "extremely long, double stranded nucleic acid molecule arranged as a double helix that is the main constituent of the chromosome and that carries the genes as segments along its strands[.]" WEBSTER'S COLLEGE DICTIONARY, 393 (1992).

The technology was novel in that it was designed to overcome many of the obstacles commonly encountered when attempting to insert foreign DNA into a host cell. Previous methods for introducing DNA into a host cell were imprecise. While millions of cells could be exposed to DNA molecules of interest, only a small proportion of the host cells absorbed and incorporated them into their own genome. Fewer still did so in a stable manner. Moreover, even if the cell incorporated the DNA molecule into its genome, it was not at all clear that descendant cells would continue to have the introduced gene or transmit it reliably from one cell generation to the next.

B. *Cotransformation Processes Claims*

1. *Cotransformation*

The various processes addressed in the Axel patents are referred to as "cotransformation." "Transformation," as defined in the patents, is a "process for changing the genotype of a recipient cell mediated by the introduction of purified DNA." The recipient cell, the one which incorporated the new DNA or gene, would be termed a "transformant." "Cotransformation" involved insertion of "more than one different gene" into the host (or recipient) cell.FN6

FN6. The parties dispute whether cotransformation is limited to the insertion of only two DNA molecules or can involve more than two. The patents define the term as merely involving "more than one different gene."

The claims themselves describe how cotransformation occurs. The first gene or DNA molecule ("DNA I") codes for the product of interest. The second gene or DNA molecule ("DNA II") codes for a substance that will be helpful in identifying and isolating the cells which have successfully incorporated these new pieces of DNA. The DNA II in the Axel patents is described as coding for a "selectable" phenotype, or in the case of claim 54 of the '216 patent, an "amplifiable gene for a dominant selectable phenotype." FN7 The patents define phenotype as "the observable properties of an organism as produced by the genotype in conjunction with the environment."

FN7. Claim 1 of the '017 patent refers to a transformed Chinese Hamster Ovary cell "which comprises amplified foreign DNA I corresponding to a gene of interest ... and amplified foreign DNA II encoding a dominant selectable phenotype...." No other independent claims refer to a "dominant selectable phenotype." The other independent claims, claims 1, 26-28, and 31 of the '216 patent, and claims 1 and 16 of the '665 patent, all refer to a DNA II coding for a "selectable" phenotype.

The patents call for the insertion of a DNA II gene which codes for something (its phenotype) that will make it possible to find cells that have acquired it and, consequently, that also have the desired properties coded for in the DNA I gene. Put more simply, the process "piggybacks" a gene that encodes a selectable phenotype (DNA II), to a gene that does not encode a selectable phenotype (DNA I) and in so doing, provides a means to select for transformed cells. Since many genes which produce proteins of commercial interest do not encode selectable phenotypes, for example, this aspect of the invention was particularly significant.

The most common selection process FN8 is to insert into the host cell, DNA II that codes for a substance resistant to a specific toxin, a substance that the host cell does not otherwise produce.FN9 Then the host cells are exposed to the specific toxin. Cells that incorporated the new DNA II survive, since they are resistant to the toxin, and, by virtue of their survival, they can be isolated and identified.

FN8. The language of the claims generally refers to selection processes that permit either the survival or the identification of the transformed cells. Presumably, some selectable (or dominant selectable) phenotypes make the cell identifiable using a technique that does not simply kill off the cells that failed to acquire the phenotype coded for in the DNA II.

FN9. The host cells used in the experiments described in the patents' specifications were both mutant and wild-type, or naturally occurring, cells. The mutant cells were cells that had been altered or mutated so that they did not produce a substance resistant to the toxin. Those same cells in their wild-type form would produce the toxin-resistant substance. In the experiments using such mutant cells, the DNA II essentially restored the mutant cell's natural ability to resist the toxin.

The Axel patents' accomplish cotransformation in one of two ways, "unlinked cotransformation claims" and "linked cotransformation." The "unlinked cotransformation claims" FN10 involve (1) the insertion of *unlinked* DNA I and DNA II into the host cell, with (2) DNA II coding for what the patent describes as a *selectable phenotype*.FN11 The "linked cotransformation claims" involve (1) the insertion of already *linked* DNA I and DNA II molecules at the time of introduction into the host cell, and (2) DNA II corresponding to an amplifiable gene for a *dominant selectable phenotype*. These are claim 54 of the '216 patent, and in a more general sense, claim 1 of the '017 patent.FN12

FN10. I only discuss the independent claims because the definitions of the dependent claims flow from the

interpretation of the independent claims.

FN11. These are claims 1, 26-28, and 31 of the '216 patent, and claims 1 and 16 of the '665 patent.

The '216 Patent Claims are the following:
Claim 1: A process for inserting foreign DNA I into a suitable eucaryotic cell which comprises cotransforming said eucaryotic cell with said foreign DNA I and with unlinked foreign DNA II which codes for a selectable phenotype not expressed by said eucaryotic cell, said cotransformation being carried out under suitable conditions permitting survival or identification of eucaryotic cells which have acquired said selectable phenotype, said foreign DNA I being incorporated into the chromosomal DNA of said eucaryotic cell.
Claim 26: A process for inserting foreign DNA I into a eucaryotic cell which comprises cotransforming said eucaryotic cell with said foreign DNA I and with unlinked foreign DNA II which codes for a selectable phenotype not expressed by said eucaryotic cell, said cotransformation being carried out in a suitable medium and in the presence of conditions permitting identification and recovery of eucaryotic cells which have acquired said selectable phenotype.
Claim 27: A process for cotransforming a suitable eucaryotic cell which comprises transforming under suitable conditions said eucaryotic cell with foreign DNA I and with foreign DNA II, said DNA I and DNA II being unlinked and said DNA II coding for a selectable phenotype not expressed by said eucaryotic cell prior to cotransformation.
Claim 28: A process for inserting purified foreign DNA I coding for proteinaceous materials which is not associated with a selectable phenotype into a suitable eucaryotic cell which comprises cotransforming said eucaryotic cell with said foreign DNA I and with unlinked foreign DNA II coding for proteinaceous material which is associated with a selectable phenotype, said cotransformation being carried out under suitable conditions permitting survival or identification of eucaryotic cells which have acquired said selectable phenotype, said foreign DNA I being incorporated into the chromosomal DNA of said eucaryotic cell.
Claim 31: A process for inserting a multiplicity of foreign DNA I molecules corresponding to multiple copies of a gene coding for a proteinaceous material into a suitable eucaryotic cell which comprises cotransforming said eucaryotic cell with said multiplicity of unlinked foreign DNA II molecules coding for a selectable phenotype not expressed by said eucaryotic cell, said cotransformation being carried out under suitable conditions permitting survival or identification of eucaryotic cells which have acquired set multiplicity of genes coding for said selectable phenotype.

The '665 Patent claims are the following:
Claim 1: A process for inserting foreign DNA I into a suitable eucaryotic cell which comprises cotransforming said eucaryotic cell with said foreign DNA I and with unlinked foreign DNA II which codes for a selectable phenotype not expressed by said eucaryotic cell, said cotransformation being carried out under suitable conditions permitting survival or identification of eucaryotic cells which have acquired said selectable phenotype, said foreign DNA II being attached to bacterial plasmid or phage DNA.
Claim 16: A process for producing a proteinaceous material which comprises cotransforming a suitable eucaryotic cell with foreign DNA I which codes for foreign proteinaceous material which is not associated with a selectable phenotype and with unlinked foreign DNA II which codes for a selectable phenotype not expressed by the eucaryotic cell, said cotransformation being carried out under suitable conditions permitting survival or identification of eucaryotic cells which have acquired the selectable phenotype, maintaining or culturing the cotransformed cells under suitable conditions permitting production of the proteinaceous material and recovering the proteinaceous material so produced.
FN12. Claim 54 of the '216 patent states:
A process for generating a multiplicity of foreign DNA I molecules corresponding to multiple copies of a

gene in a cell with a molecule which comprises transforming said eucaryotic cell with a molecule which is formed by linking one of said DNA I molecules to a DNA II molecule corresponding to an amplifiable gene for a dominant selectable phenotype not expressed by said eucaryotic cell, and culturing the transformed eucaryotic cells in the presence of successively elevated concentrations of an agent permitting survival or identification of eucaryotic cells which have acquired multiple copies of said amplifiable gene, said transformation and culturing being carried out under suitable conditions.

Claim 1 of the '017 patent refers to amplified DNA coding for a dominant selectable phenotype though it does not explicitly state that the DNA I and DNA II are linked prior to introduction into the cell:

A transformed Chinese Hamster Ovary cell which comprises amplified foreign DNA I corresponding to a gene of interest stably incorporated into the chromosomal DNA of the transformed cell and amplified DNA II encoding a dominant selectable phenotype not expressed by the transformed cell prior to transformation.

2. ***The Significance of Amplification***

The most significant difference between the linked and unlinked cotransformation claims concerns the role of amplification.FN13 The latter results in an increase in the number of copies of DNA I, one of the innovations of the Axel patent.FN14

FN13. This discussion should not be taken to suggest that there are no material differences amongst the unlinked cotransformation claims. Instead, I focus on the commonalities of these claims and how these claims differ from certain features of the claims involving linked cotransformation.

FN14. As Weinberg explains:
the two genes are physically linked to one another prior to introduction of the cell. And that type of linkage is, in the great majority of cases, strongly preserved. It's a strong linkage. So that the amplification will almost certainly ensure the coamplification of the DNA I gene.

Indeed, Webb referred to the both the [co]amplification of the inserted genes and the linkage of the genes prior to insertion as part of the "novelty of the Axel patents." Weinberg also noted that the use of the DHFR gene to encourage the coamplification of DNA I "represented the power of this process" which "had not been done previously."
In the unlinked cotransformation claims, the acquisition of a single copy of the DNA II (coding for resistance to the toxin) is sufficient for the cell to survive when exposed to that toxin.FN15 In the linked cotransformation process described in claim 54 of the '216 patent, a single copy of the DNA II (an amplifiable gene) would not be enough for the particular cell to survive the selection processes covered by this particular claim. Claim 54 of the '216 patent explicitly states that the selection process involves "culturing the transformed eucaryotic cells in the presence of successively elevated concentrations of an agent permitting survival or identification of eucaryotic cells which have acquired *multiple copies* of said amplifiable gene [.]" FN16

FN15. For example, claim 1 of the '216 patent states that the host cells survive (or can be identified) if they have acquired the selectable phenotype coded for by the DNA II. The claim does not call for multiple copies of the DNA II to be incorporated in order for the host cells to survive (or be identified). This is in stark

contrast to claim 54 of the '216 patent.

FN16. In discussing the series of experiments involving this particular process, the patentees make clear that, "[e]xposure of these initial mtx resistant transformants to stepwise increases in drug concentration results in the *selection of cells with enhanced mtx resistance resulting from amplification of the newly transferred mutant hamster dhfr gene*." (emphasis added).

The multiple copies called for in claim 54 result from the process of amplification-increasing the number of copies ("copy number") of the amplifiable gene.FN17 While the amplifiable gene used in the experiments discussed in the patents' specification was a mutant dihydrofolate reductase gene ("DHFR"), the claim language does not require the use of any specific amplifiable gene.FN18 "Mutant DHFR" refers to a gene that is not in its naturally occurring state, but in a mutant or altered form. DHFR is an amplifiable gene whether it is in its mutant form or its "wild" form-meaning its naturally occurring form.FN19

FN17. While Webb notes that multiple copies can also result from multiple insertions of that gene (Webb even states that he believes multiple insertion could be a type of amplification), that is clearly not the process called for by the claim language or utilized in the experiments discussed in the specification.

FN18. According to Weinberg, there are relatively few amplifiable genes that can work in conjunction with a metabolic antagonist in a similar manner to DHFR. This is consistent with the specification which states, "[a]lthough various amplifiable genes for dominant selectable phenotypes are useful in the practices of this invention, genes associated with drug resistance, e.g., the gene for dihydrofolate reductase which renders cells resistant to methotrexate, are particularly suitable."

FN19. Webb testified that the mutant DHFR gene produces a slightly different form of the DHFR protein than the wild DHFR gene. According to Webb, this protein provides an improved level of resistance to the growth inhibitory mechanism present in the toxin used in conjunction with genes coding for DHFR. This testimony is also consistent with the patent, "[i]t is likely that a single mutant gene affords significantly greater resistance to a given concentration of mtx than a single wild-type gene."

The gene is considered amplifiable because it increases the number of copies inside the transformed cell in response to an alteration of the culture medium.FN20 In the case of DHFR, that copy number increases when exposed to the toxin, methotrexate ("MTX"). Indeed, the relationship between MTX and DHFR is antagonistic. MTX is lethal to cells that do not have enough copies of the DHFR gene, but it also causes cells to increase their copy number of the DHFR gene, perhaps sufficient to enable their survival. MTX is the toxin that would be used in the selection process when the DNA II codes for DHFR.

FN20. The parties have slightly different definitions of an amplifiable gene. Columbia would define it as genes that increase copy number in response to a manipulation by the operator of a process, which would also include an alteration of the culture medium. Roche's definition is limited to increases in copy number in response to alterations of the culture medium.

This process of amplification, through exposure to successively elevated concentrations of the toxin, makes possible a selection process that selects for only those cells with multiple copies of the amplifiable gene. And where the DNA I molecule is physically linked to the DNA II molecule (when exposed to the

appropriate agent) *both* genes are amplified.FN21 Use of this process increases the number of copies of DNA I even though the DNA I is not an amplifiable gene.FN22 This increases a cell's potential production of the desired product coded for in the DNA I.

FN21. While the parties offer slightly different interpretations of the linking of the DNA I with the DNA II, neither side disputes that the linkage of DNA I with an amplifiable gene (DNA II) induces the amplification of that DNA I even though it is not an amplifiable gene.

FN22. This is also consistent with the specification and the prosecution history. The patentees report that, "amplification of the dhfr genes results in amplification of pBR322 sequences [presumably DNAI which is not normally amplifiable] ..." The prosecution history also indicates that the process selects for cells "which have acquired multiple copies of the amplifiable gene and thereby multiple copies of foreign DNAI ..."

3. ***Expandinq Potential Host Cells***

The coamplification of both the DNA I and DNA II was not the only significant advance of the Axel patents. The inventors were able to expand the range of potential host cells available for cotransformation processes. The linked cotransformation claims clearly made possible the use of wild-type host cells, as the experiment discussed in the specification discusses:

In the present study, a dominant acting, methotrexate resistant dhfr gene has been transferred to wild-type cultured cells. The use of this gene as a vector in cotransformation systems may now permit the introduction of virtually any genetic element into a host of new cellular environments.

4. ***Contested Claim***

The most significant issue in this hearing is the meaning of the words "selectable phenotype" as used in the unlinked cotransformation claims as compared to amplifiable gene for "dominant selectable phenotype" used in the linked cotransformation claims. The parties vigorously dispute whether the eucaryotic host cell discussed in the linked cotransformation claims is limited to only wild-type eucaryotic cells or can include mutant eucaryotic cells as well. While both sides agree that the process would work in both, Roche believes the specific language Columbia used in claim 54-the addition of the word "dominant" to the words "selectable phenotype"-somehow limits its coverage to processes involving wild-type cells, even though no such limitation exists in all of the other Axel claims. Columbia claims that what is distinctive about the linked cotransformation claims, the coamplification, covers both mutant or wild-type eucaryotic cells.

C. ***Product by Process Claims***

The '216 patent also includes another type of claim, commonly referred to as a product by process claim. These claims are for products that are defined by the process used to create them. For example, two product by process claims of the '216 patent provide:

Claim 72: A eucaryotic cell into which foreign DNA I has been inserted in accordance with process of claim 54.

Claim 73: A mammalian cell into which foreign DNA I has been inserted in accordance with the process of claim 54.

The cell claimed in each patent is defined by the process described in claim 54 of the '216 patent. According to Weinberg's uncontroverted testimony, cells created in accordance with the process described in claim 54

of the '216 patent "presumably never existed naturally in the biosphere." These cells have been altered to have multiple copies of both DNA I and DNA II in their genotype. Whether this novel biological product, the transformed cell with multiple copies of both DNA I and DNA II, can be claimed in the patent without regard to the process used to create it, is the second major issue of claim interpretation which the Court must resolve.

This issue is purely a question of law. As such, I will deal with the parties arguments on this issue solely in the analysis section of this opinion.

II. *ANALYSIS*

The parties have extensively briefed two issues of claim construction which I shall address in turn. While there are other minor areas of dispute concerning the proper interpretation of the claim language, the parties have relied primarily on their claim construction charts as identifying the support for their respective positions. The definitions the Court has adopted for all the disputed terms appear in a similar chart format at the close of this opinion.

A. *The Rules of Claim Construction*

[1] When interpreting the claims of a patent, the Court is to first consider intrinsic evidence, which includes the patent claims themselves, the patent specification, and the prosecution history of the patent application before the United States Patent and Trademark Office. Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir.1996). The intrinsic evidence "is the most significant source of the legally operative meaning of disputed claim language." *Id*. The order of consideration is first, the language of the claims, then the specification, and, finally, the prosecution history. *Id*.

The role of the specification is particularly important; "it is the single best guide to the meaning of a disputed term." *Id*. "The specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication." *Id*. The prosecution history contains the record of the proceedings before the Patent and Trademark Office and "is often of critical significance in determining the meaning of the claims." *Id*.

[2] [3] When the intrinsic evidence "unambiguously describes" the scope of the patented invention, it is improper to rely on any extrinsic evidence. *Id*. at 1583. It is, after all, the intrinsic evidence that is the public record of the patentee's claim, on which competitors are entitled to rely. *Id*. They are to review that record, apply the established rules of claim construction to determine the scope of the invention and then design around it. *Id*. At the same time, extrinsic evidence may be used if it is needed to assist in determining the meaning of technical terms used in the claims, but not to alter their meaning. *Id*.

B. *The Parties' Positions on the Issue of a Dominant Selectable Phenotype, and Their Evidence and Arguments in Support of Those Positions*

[4] The major claim construction dispute involves the language in claim 54 of the '216 patent. Claim 54 states:

A process for generating a multiplicity of foreign DNA I molecules corresponding to multiple copies of a gene in a *eucaryotic cell* which comprises transforming said *eucaryotic cell* with 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 selectable phenotype* not expressed by said *eucaryotic cell,* and culturing the transformed *eucaryotic cells* in the presence of successively elevated concentrations of an agent permitting survival or identification of *eucaryotic cells* which have acquired multiple copies of said *amplifiable gene,* said transformation and culturing being carried out under suitable conditions.

(emphasis added). Specifically, the parties contest the meaning of the phrase "an amplifiable gene for a dominant selectable phenotype," and by implication, the meaning of "eucaryotic cell" (at least as referred to in claim 54 of the '216 patent).

Roche argues that a *dominant* selectable phenotype must mean something different than a selectable phenotype, since "dominant" is modifying the word "selectable." That difference, according to Roche, is this: The "amplified" gene that codes for the dominant selectable phenotype is always used in the patent in connection with the transformation of a wild-type host cell, never the transformation of a mutant cell.FN23 A dominant selectable phenotype, it argues, has to be inserted into a wild-type host cell so that it has a wild-type genome to "dominate."

FN23. Roche's proposed definition of "dominant selectable phenotype" reads as follows: "A property of a cell which allows that cell to survive under conditions lethal to a wild-type cell."

Columbia claims that a "dominant selectable phenotype" should simply be read as a phenotype involving an amplifiable gene. The claims, it suggests, refer to "dominant selectable phenotypes" only in the context of processes utilizing amplification.FN24 And in that setting, *both* mutant and wild-type host cells would qualify. In any event, Columbia argues that it would make no sense to define the eucaryotic host cells described in claim 54 as limited to only wild-type cells while interpreting eucaryotic cells without regard to mutant/wild form in all other claims.

FN24. Columbia's definition links the concept of a dominant selectable phenotype to the use of an amplifiable gene by linking the survival of a cell to having acquired sufficient copy number of the gene: "A selectable phenotype which allows an organism or a cell of a defined genotype that acquires such phenotype, e.g. as a result of introducing a gene at a suitable copy number, to survive while other organisms or cells of the same defined genotype which have not acquired such phenotype will not survive or proliferate."

Roche advances a series of arguments in support of its interpretation:

1) The claims "expressly distinguish" between "selectable" and "dominant selectable" as claims 1-53 of the '216 patent and all of the claims of '665 patent *exclusively* use the term "selectable," whereas claims 54-73 of the '216 patent *exclusively* use the term "dominant selectable."

2) In the specification, "dominant selectable" always describes transformation of wild-type cells and never describes the transformation of mutant cells.

3) The experiments described in the patent that used mutant host cells never refer to the foreign DNA as coding for a "dominant" selectable phenotype or as a dominant acting marker, whereas the experiments involving wild-type cells refer to the foreign DNA as a dominant-acting gene.

4) The inventor's publications (incorporated by reference into the patents) describe experiments using mutant host cells where the markers are described as selectable and/or recessive, and further state that these markers can only be used in mutant host cells.

5) The prosecution history of the '216 patent shows that the inventors distinguished their claim from prior art involving the cotransfer of two linked human genes in eucaryotic cells by indicating that the prior art did not "teach or suggest transforming eucaryotic cells with a DNA molecule that is formed by linking a foreign

DNA I molecule, containing a gene encoding a protein, to a DNA II molecule which corresponds to an amplifiable gene for a dominant selectable phenotype ..."

6) Interpreting the claims as Columbia proposes would render some claims invalid in light of prior art that successfully incorporated multiple copies of linked genes in transformed eucaryotic cells as early as 1975.

Roche's first four arguments are inferences from the coincidence of certain words. Roche asks the Court to infer a limitation on the type of eucaryotic cell that can be used as host cells in claim 54 because the words "dominant selectable" or "dominant acting" are always used when discussing cotransformation processes involving wild-type host cells in the claims, the specification, the descriptions of the experiments in the specification, and, the publications of the inventors (incorporatedby reference into the specification).

At the same time, Roche concedes that no intrinsic evidence explicitly announces that limitation-that a dominant selectable phenotype *cannot* be used with a mutant host cell. Indeed, nowhere in the claim language do the words "wild-type cell" even appear. Rather, Roche argues that such consistent usage of the term with wild-type cells is not an accident, but reflects a *de facto* limitation inherent in the word "dominant."

Columbia's approach is the same but its conclusions are different. Because the phrase "dominant selectable phenotype" is invariably used in conjunction with the phrase "amplifiable gene," it is that trait that defines the phrase. Here again, nothing in the intrinsic evidence explicitly states that a dominant selectable phenotype *must* be associated with a process using an amplifiable gene. Like Roche, Columbia asks the Court to infer this from the juxtaposition of the two phrases.

As described below, Columbia has the better of the argument.

1. *Claim Language*

The claim language specifically describes in great detail a process of selection which requires the amplification, or increased copy number of, the amplifiable gene. Indeed, amplification is a central part of the patent's innovation.

In contrast, there is no mention in the claim language of the distinction Roche presses, between eucaryotic mutant host cells and eucaryotic wild-type host cells. Moreover, as described below, such an interpretation seems to unreasonably convert what was described as the innovative capability of the process-that it would work on wild-type host cells-into a limitation. The more logical inference is that the patentees associated a dominant selectable phenotype with the use of an amplifiable gene, whether it be with a mutant or wild-type host cell.

2. *The Specification*

Roche seeks out further support from the patent specification of the '216 patent. It relies primarily on this paragraph:

Cotransformation with *dominant-acting markers* should in principle permit the introduction of virtually any cloned genetic element into *wild-type* cultured eucaryotic cells. To this end, a *dominant-acting* methotrexate resistant, dihydrofolate reductase gene from CHO A29 cells was transferred to *wild-type* cultured mouse cells.... The use of this gene as a *dominant-acting* vector in eucaryotic cells will expand the repetoire [sic] of potentially transformable cells, *no longer restricting these sort of studies to available mutants*. (emphasis added).

Focusing on the language of this paragraph, Roche argues:

The distinction that the phenotype, or the gene that encodes the phenotype, is variously described in the patent as either selectable or dominant selectable is clearly related to the phenotypic background, i.e., mutant versus wild-type, of the cells into which the DNA is being incorporated. *It is only where the foreign gene is inserted into a wild-type background with respect to the phenotype being assayed for that the foreign gene is referred to as a dominant-acting selectable marker or encoding a dominant selectable phenotype*. (emphasis in original).

I do not find that this language, especially when considered in the context of the remainder of the specification, demonstrates what Roche proposes, and hardly demonstrates it "clearly."

The final sentence states that use of the marker expands the range of potential host cells, *no longer restricting* them to mutant cells. This suggests that the dominant marker technique includes a range of host cells beyond, yet including, mutant cells. It does not suggest a restriction at all.

Moreover, the specific mention of wild-type cells in conjunction with the linked cotransformation process is not surprising because (1) it trumpets an advance of the patents, and (2) it references an experiment that is discussed later in the patent. As Webb, Roche's expert, testified:

the problem with [an older] system is it limits you somewhat in the utility of the procedure. You have to have this very unusual condition of a mutated cell. What people clearly wanted to do was to use this technique of transformation in *any* cell type, and so the utility of the procedure would be greatly enhanced were that possible. (emphasis added).

That was precisely the market, if you will, to which this invention was directed. It was directed towards having an essentially unlimited, an unrestricted supply of the type of cells into which one could make the transfer carry out the selection in a normal cell, not a specialized cell that one had to hunt high and low for. You could just take any cell, so-called primary cells, the normal cells from normal tissues of human beings, for that matter, and to carry out the selection.FN25

FN25. My recitation of Webb's expert testimony should not be taken as a retreat to extrinsic evidence. I merely note it to show that neither party contests this position. The very same information is articulated in the patent itself: "Cellular genes coding for selectable biochemical functions have previously been introducted [sic] into mutant cultured cells ... In the present study, a dominant acting, methotrexate resistant dhfr gene has been transferred to wild-type cultured cells. The use of this gene as a vector in cotransformation systems may now permit the introduction of virtually any genetic element into a host of new cellular environments."

Simply because the "market" demands a process with a particular capability does not mean that the process should, by definition, be limited to only that capability and no other-especially without any explicit statement suggesting that it be so limited.FN26

FN26. Indeed, in discussing the claims of the '216 patent generally, there are over thirty references to the host cells being eucaryotic cells without ever suggesting that certain claims cover different types of eucaryotic cells than other claims. If such a distinction existed in the minds of the patentees, it surely would have been expressed explicitly.

The remainder of Roche's argument with respect to the specifications relies on the same type of inference

argument that Roche made with respect to the claim language. The argument is equally unavailing for similar reasons.

In any event, Roche's inference argument is significantly weakened when considering it in the context of the entire specification. In describing the linked cotransformation claims, the term wild-type cells only appears in the two instances cited by Roche-one of which merely refers to an experiment that is described later in the patent. In every other instance (the Court counts nine other instances) in which the linked cotransformation claims are discussed, the host cells are invariably described as eucaryotic cells with no reference to wild or mutant form-just as in the actual language of the claims.

In fact, the specification suggests the very opposite of what Roche proposes. The patentees clearly intended the term eucaryotic cell to cover the broadest range of cells possible without regard to: (1) which of the individual claims were involved, (2) the experiments discussed in the patent, and (3) the form, i.e. mutant or wild, of the eucaryotic cell:

Although the experiments discussed hereinafter concern cultured eucaryotic cells of mammalian origin such as human blood cells, mouse fibroblast cells, chinese hamster ovary cells and mouse teratocarcinoma cells, it is clear that the process described is generally applicable to all eucaryotic cells including, for example, cells from birds such as chickens, cells from yeast and fungi, and cells from plants including grains and flowers. Therefore, it is to be understood that the invention encompasses all eucaryotic cells even though the invention may ultimately be most useful in cotransforming mammalian cells.

If the patentees intended certain claims to cover certain types of eucaryotic cells and not others, such a limitation would surely have been included in the above paragraph defining the scope of eucaryotic cell. Instead, the quoted text suggests that eucaryotic cell means *all* eucaryotic cells, and, significantly, regardless of whatever types of cells are used in the experiments discussed later in the patent. Again, this paragraph, which is the only paragraph dedicated to describing what types of host cells are covered by the term eucaryotic cell, does not even hint of a distinction with respect to mutant vs. wild-type form.

[5] Moreover, adopting a more limited definition of eucaryotic cell than the ordinary meaning (which would make no distinction with respect to mutant or wild form) for some of the patent claims would also be inconsistent with the rules of patent construction. There is a heavy presumption in favor of the ordinary meaning of a term. *See* Johnson Worldwide Associates, Inc. v. Zebco Corp., 175 F.3d 985, 990 (Fed.Cir.1999) (two situations permit deviation from the ordinary meaning of a term: (1) "the patentee has chosen to be his or her own lexicographer by clearly setting forth an explicit definition for a claim term"; and, (2) "where the term or terms chosen by the patentee so deprive the claim of clarity that there is no means by which the scope of the claim may be ascertained from the language used.") (citations omitted).

In this case, the patentees do not offer a definition for eucaryotic cell different from its ordinary meaning. Nor does use of the terms "amplifiable gene for a dominant selectable phenotype" in any way deprive the claim of clarity. On the contrary, the most logical inference is Columbia's: that dominant selectable phenotype is associated with an amplifiable gene, and its use in connection with eucaryotic cells does not alter its common meaning.

Finally, one need only look to the patentees' treatment of the term "selectable phenotype" for further support.

First, "selectable phenotype" like "dominant selectable phenotype" is defined in the claims without reference to whether the host cell in question is wild-type or mutant. Roche, however, agrees that the former can be used with either while in the case of the latter, it maintains only wild-type host cells are contemplated.

Second, the experiments described in connection with a "selectable phenotype" use only mutant host cells. Nevertheless, Roche agrees that the claim language pertaining to "selectable phenotypes" should not be so limited. Again, it takes a different position with respect to "dominant selectable phenotypes."

Third, at one point in the specification the patentees describe mutant DHFR (which everyone agrees is also a "dominant selectable phenotype") as an example of a selectable phenotype. This cannot be reconciled with Roche's position-that selectable phenotypes can be used with both types of host cells while dominant selectable phenotypes are more limited.

The definition of "selectable phenotype" found in the specification states:

selectable phenotype is a phenotype which confers resistance upon an organism [sic] ability to exist under conditions which kill off all organisms not possessing the phenotype.... (italics in original).

In addition, the specification notes:

a DNA II which includes a gene coding for a *selectable phenotype* associated with drug resistance, e.g., a *mutant dihydrofolate reductase gene* which renders cells resistant to methotrexate greatly extends the applicability of the process. (emphasis added).

In short, Roche's definitions are inconsistent with the rules of claim construction, "[v]aried use of a disputed term in the written description demonstrates the breadth of the term rather than providing a limited definition." Zebco Corp., 175 F.3d at 991 (citations omitted). Here, a gene coding for a dominant selectable phenotype is also referred to as a gene coding for a selectable phenotype. The word dominant cannot impose a limitation, but rather, must demonstrate the breadth of the term, i.e., genes coding for a dominant selectable phenotype, such as a mutant DHFR gene, can also code for a selectable phenotype.

Reading the specification in its entirety, several things are clear: (a) When discussing the claims of the '216 patent generally, the specification uniformly discusses eucaryotic host cells without regard to whether they are in mutant or wild form. Indeed, the language suggests that the patentees intended to include the broadest possible range of host cells permitted by the term eucaryotic cell, without differentiating between the various claims of the patent. (b) There is simply nothing in the specification which suggests that the patentees intended eucaryotic cells to mean anything other than its ordinary definition. (c) Nor is there any support for Roche's attempt to limit the meaning of eucaryotic host cells by use of the term dominant selectable phenotype. The patentees clearly did not define selectable phenotype with reference to the type of host cell, and there is no reason to think the patentees would have defined dominant selectable phenotype in that manner either.

For all these reasons, the language of the specification favors Columbia's proposed claim construction.

3. *The Experiments Described in the Patents*

Roche's argument with respect to the descriptions of the experiments repeats the same themes:

There are a total of five series of experiments in the '216 patent. In four out of those 5 ..., there is transfer of foreign DNA (the TK gene) into a mutant cell line ... This foreign DNA is never referred to as a dominant acting marker or encoding a dominant acting marker or encoding a dominant selectable phenotype. It is always referred to as a selectable marker or encoding a selectable phenotype. In stark contrast, in the remaining series of experiments ... where the co-transformation of wild-type, non-mutant cells is described, the foreign gene responsible for encoding a selectable phenotype FN27 is referred to as a dominant acting gene.

FN27. While attorney argument is certainly not evidence, I should note for the record that counsel for Roche has argued that the "dominant-acting" gene mentioned in the experiments using wild-type cells encoded for only a "selectable phenotype." Under Roche's definition of the term, however, a dominant-acting gene could never code for a "selectable phenotype" because selectable phenotypes may be used with mutant host cells (unlike dominant selectable phenotypes). Roche's counsel actually makes this error twice in the section of its brief discussing the experiments.

Once again, the consistent use of the term "dominant" with cotransformation using wild-type cells can just as easily be explained by its consistent association with an amplifiable gene, which Columbia emphasizes. The TK gene, or gene for thymidine kinase, which is the gene used in the four experiments where the term dominant is *not* used, is not an amplifiable gene. The remaining series of experiments, which did use the term dominant, used a mutant DHFR gene, which is an amplifiable gene. However, there is additional language in this section which favors Columbia's interpretation.

In the section entitled "THE dhfr GENE AS A GENERALIZED TRANSFORMATION VECTOR," the mutant DHFR gene (which Roche argues is a dominant acting gene, or marker, rather than a selectable marker like the TK gene) is twice referred to as merely "selectable":

The generality of this approach was tested for the *selectable marker,* the mutant dhfr gene.

An alternate approach to generalized transformation involves ligation of a nonselectable DNA sequence to a *selectable gene*. Since the muant [sic] dhfr gene is a *dominant acting* drug resistance [sic] factor, this gene is an ideal vector. (emphasis added).

There simply is no way to reconcile this language with Roche's proposed claim construction that the term dominant, unlike the term selectable, must go hand in hand with wild-type cells (and consequently, never mutant cells). In short, "dominant-acting gene" and "selectable gene" are used interchangeably.

There are additional passages in this section of the patent which suggest that the term dominant does not impose any limitation on the type of host cells that may be used in cotransformation:

Furthermore, the use of dominant acting mutant genes which can confer drug resistance will extend the host range for cotransformation to virtually any cultured cell.

In this way it is possible to transfer and amplify virtually any genetic element in cultured mammalian cells.

Nevertheless, it appears that the mutant dhfr gene can be used as a vector for the introduction and amplification of defined DNA sequences into cultured animal cells.

The use of this gene as a vector in cotransformation systems may now permit the introduction of virtually any genetic element into a host of new cellular environments.

None of these selections even hint of a limitation on using dominant selectable phenotypes with wild-type host cells.

Finally, at two points in the specification, the patentees stress that the experiments should be taken as examples only, and not as limitations on the broader claim language. The first is one which I mentioned with respect to the scope of the eucaryotic cell, where the patentees clearly state, "[a]lthough the experiments discussed hereinafter concern cultured eucaryotic cells of mammalian origin such as ..., it is

clear that the process described is generally applicable to all eucaryotic cells ..." The second occasion references experiments using mouse fibroblast cells:

Cotransformation in accordance with this invention may be carried out in any suitable medium limited only in that cotransformed cells be capable of survival and/or identification on the medium. *Merely by way of example,* a suitable medium for mouse fibroblast cells which acquired the thymidine kinase gene in HAT is described more fully hereinafter. (emphasis added).

The experiments were not meant to provide limitations on the broader language used in the claims.

4. ***The Inventors' Publications***

Roche makes a similar argument with respect to two of the inventor's publications, both of which are incorporated by reference into the patent. Roche begins by noting that the gene coding for TK, or thymidine kinase, is never associated with the term dominant, and in fact, on one occasion, is referred to as a recessive marker-requiring that it be used with mutant host cells. Still it acknowledges that the unlinked cotransformation claims using selectable phenotypes cover processes using both mutant and wild-type host cells.

And in the very same article referring to these markers as recessive, in fact, in the very next sentence, the inventors make clear that dominant markers are *capable* of using, *but not restricted* to using, non-mutant host cells:

The ability to transfer dominant-markers is *not restricted to specific mutant cells* and would greatly extend the usefulnessof the transformation technology.

(emphasis added). Nothing in this article suggests any reason to limit dominant-markers to cotransformation processes using only wild-type cells.

In the other article to which Roche appeals, a similar sentence follows the one quoted by Roche:

The use of such dominant acting mutant genes which confer drug resistance may extend the host range for co-transformation to *virtually any cultured cell*. While these articles might provide some support for a position that neither party adopts (that selectable markers must only be used with mutant cells), they certainly provide no support for the position that dominant genes or dominant markers must only be used with wild-type host cells.

5. ***Prosecution History and Prior Art***

Roche's final attempt to bolster the evidence in support of its claim construction looks to the prosecution history and prior art arguing that (1) the term dominant selectable phenotype was needed to overcome a prior art objection by the Patent and Trademark Office, and (2) that Columbia's proposed interpretation of dominant selectable phenotype would render some of the claims invalid in view of the prior art.

Roche argues that the patentees were able to overcome the Patent and Trademark Office's objection based on prior art by Willecke, et. al., by pointing to the use of a dominant selectable phenotype. This is simply unsupported by the prosecution history. The objection based on Willecke, et. al. reads in its entirety:

Willecke et al [sic] teach the cotransfer of two linked genes into cultured mouse cells using one gene coding for a selectable trait and producing proteins from each gene.

The patentees' full response reads:

Willecke et [sic] al. teach the cotransfer in eucaryotic cells of a segment of chromosomal DNA from human lymphoblastoid cells which contains two linked human genes. Willecke et [sic] al. do not teach or suggest transforming eucaryotic cells with a DNA molecule that is formed by linking a foreign DNAI molecule, containing a gene encoding a protein, to a DNAII molecule which corresponds to an amplifiable gene for a dominant selectable phenotype which is not expressed by the eucaryotic cell, as in applicants claim 153. Furthermore, Willecke et [sic] al. do not teach or suggest culturing elevated concentrations of an agent permitting identification of eucaryotic cells which have acquired multiple copies of the amplifiable gene and thereby multiple copies of foreign DNAI, as in applicants' claim 153. Willecke et [sic] al. do not teach or suggest the use of a DNA II which encodes an amplifiable gene for a dominant selectable phenotype as a means of identifying eucaryotic cells which have been amplified to contain multiple copies of a foreign DNAI.

The patentees raise numerous distinctions other than the use of the term "dominant selectable phenotype": (1) the prior art did not link the two genes, (2) the prior art did *not* use an amplifiable gene for a dominant selectable phenotype, (3) the prior art did not involve culturing the transformed cells in successively elevated concentrations of an agent that permits the selection of cells which have acquired multiple copies of both the amplifiable gene and the DNAI, and, somewhat related, (4) the prior art did not use an amplifiable gene for a dominant selectable phenotype as a means of identifying eucaryotic cells which have been amplified to contain multiple copies of a foreign DNAI. Again, while the term dominant selectable phenotype appears in the patentees' response to the objection, it never appears apart from the term amplifiable gene.

More significantly, there is a conspicuous absence of any reference to either wild-type host cells in the Axel invention, or mutant host cells in the prior art. In fact, the prior art is described by the patentees in their objection as involving *eucaryotic* cells, generally. Roche's prosecution history argument is simply without merit.

Roche's final argument is an invalidity argument based on the prior art. Roche relies on Webb's expert report to argue that the claims in question would be invalid if the term dominant selectable phenotype were defined without regard to the phenotypic background of the host cell. In support of this position, Webb identified prior art by Kraiselburd and colleagues which he reports involved the transformation of TK- (mutant) cells with the gene for TK that resulted in multiple copies of the TK gene and other genetic information, when using the "kinetics of hybridization between radioactively tagged HSV DNA and cellular DNA isolated from TK+ transformants." Though the specifics of the prior art by Kraiselburd are difficult to glean from the scant information provided by Webb, it is clear that (1) Kraiselburd did not utilize an amplifiable gene, and (2) the multiple copies of the genetic information were not the result of using an amplifiable gene which increases its copy number upon exposure to successively elevated concentrations of an agent permitting survival or identification of those cells which have acquired multiple copies of the amplifiable gene. This argument is also without merit.

After a thorough review of the arguments made by both sides, and an extensive examination of the intrinsic evidence, I conclude that Columbia's position (which links dominant selectable phenotype to the use of an amplifiable gene) is the most proper way to define the term, and that Roche's proposed construction is unsupported by the intrinsic evidence, including the prosecution history. The Court's definition of the term appears in the claim construction chart appearing at the close of this opinion.FN28

FN28. While the Court feels that reliance on the extrinsic evidence presented is not necessary to define the term at issue, I note that nothing in that testimony would alter the conclusion or even cast doubt upon the Court's conclusion. The testimony of Webb and Weinberg was not only inconsistent vis-a-vis each other,

but was inconsistent with both parties' proposed claim construction. Moreover, each recognized that scientists' understanding of the terms at issue were not uniform. Given that ambiguity, strict adherence to the intrinsic evidence would have been even more appropriate.

C. *Product by Process: Limited to the Process or Not?*

[6] As I discussed earlier, whether a product by process claim is limited to covering only products made with the identical process described in the claim is a question of law. The Federal Circuit has been less than helpful in providing guidance on the issue. In a 1991 case involving biotechnology dealing with the ultrapurification of blood clotting factor using monoclonal antibodies, a three judge panel held that the "correct reading of such product-by-process claims is that they are not limited to product prepared by the process set forth in the claims." Scripps Clinic & Research Foundation v. Genentech, Inc., 927 F.2d 1565, 1583 (Fed.Cir.1991). One year later, involving patents dealing with shoe innersoles. a different three judge panel held the opposite, that the process described is essentially a limitation on the product claimed. Atlantic Thermoplastics Co., Inc. v. Faytex Corp., 970 F.2d 834 (Fed.Cir.1992) *reh'g en banc denied,* 974 F.2d 1299 (concurring opinion), 974 F.2d 1279 (dissenting opinion) (Fed.Cir.1992). In other words, the *Atlantic Thermoplastics* panel held that there could be no infringement unless the same process was used.

The *Atlantic Thermoplastics* decision was denied rehearing en banc with several dissenting judges, one of which described the decision as "mutiny," "heresy," and "illegal" for its casual dismissal of the *Scripps* decision in a footnote-for *Scripps*' alleged failure to consider SupremeCourt precedent. Atlantic Thermoplastics, 974 F.2d at 1281. The dissent argued that the original *Atlantic Thermoplastics* panel decision failed to recognize that a true product-by-process claim involves a completely novel and unobvious product, regardless of whether the process used to make it is patentable. Id. at 1282. According to the dissent, these types of claims are useful when "the invention is a chemical or biological product of such structural complexity that the product can not be defined in independent structural terms." *Id*. The dissent argued that the claim before the original panel was not a true product by process claim, and that the panel had essentially misinterpreted a century of case law, assembling "a collection of dicta lifted out of context, until a new structure has been built on the most tenuous of supports." *Id*. at 1296. The concurring opinion to the denial of rehearing en banc defended the original panel decision on essentially the same grounds it was decided.

Plainly, the law on this issue is in a state of uncertainty. By denying the rehearing en banc, not only are lower courts left with little guidance, but so are the inventors and investors of the biotechnology and pharmaceutical industries who must make research and development decisions not knowing how much protection is available to a claim for a novel biological or chemical product. On both sides of the debate, there are policy arguments as to which rule will promote more innovation and progress.

As a lower court, however, I cannot simply choose the rule which I deem the better policy. *See* Tropix, Inc. v. Lumigen, Inc., 825 F.Supp. 7 (D.Mass.1993) (holding that "while there is much to be said as a matter of policy [for the *Scripps* rule] ... particularly in the present age of rampant biotechnology," the *Atlantic Thermoplastics* rule should apply). In reaching its decision, the Court in *Tropix* stated that "[i]t would appear to me, even in the confused state of the record, that a majority of the judges of the Federal Circuit would rule that *Atlantic* states the controlling law, and I so rule in this case." Id. at 10.

I do not share the *Tropix* Court's confidence that the votes of the Federal Circuit can be so easily predicted. Two panel opinions are in direct conflict. It is impossible to divine the reasons why the various judges voted for a denial of a rehearing en banc.

[7] While this leaves the Court in an unenviable position with respect to the appropriate ruling on the merits,

there is Federal Circuit case law which offers clear guidance to escape the dilemma. When confronted with two panel opinions in direct conflict, the earlier decision is controlling. *See* Texas Instruments v. Cypress Semiconductor Corp., 90 F.3d 1558 (Fed.Cir.1996); Newell Companies, Inc. v. Kenney Mfg. Co., 864 F.2d 757, 765 (Fed.Cir.1988). Until the *Scripps* decision is rejected by a hearing en banc, it is the precedential decision. *Id*. This Court is not alone in adopting this approach with respect to this very conflict regarding product by process claims. *See* DeKalb Genetics Corp. v. Northrup King Co., No. 96 C 50169, 1997 WL 587492 (N.D.Ill. Aug.14, 1997).

Accordingly, the product by process claims shall be interpreted so that "they are not limited to product prepared by the process set forth in the claims." Scripps, 927 F.2d at 1583.

III. ***CLAIM CONSTRUCTION CHART ADOPTED BY THE COURT DEFINING DISPUTED CLAIM LANGUAGE***

TERM	**COURT'S CONSTRUCTION**
Amount Relative	The ratio of foreign DNA I to foreign DNA II
Amplifiable Gene	DNA corresponding to a gene whose copy number will increase inside a transformed cell in response to manipulation by the operator of a process
Amplified Foreign DNA I	Foreign DNA I corresponding to a gene of interest that is present in a cell in increased copy number as a result of gene amplification in the cell
Amplified DNA II	DNA II that is present in increased copy number in a cell as a result of gene amplification in the cell and confers a selectable phenotype of proliferative advantage under specific conditions of culturing the cell, enabling selection of cells which carry an increased copy number DNA II
Chinese Hamster Ovary Cell	A cultured eucaryotic cell originating from the ovary of a Chinese hamster
Cotransformed Eucaryotic Cell	A eucaryotic cell that has undergone a genotypic change as a result of the introduction into the cell of more than one different or distinct genes
Cotransforming	Process for carrying out transformation of a recipient cell with more than one different or distinct gene. Cotransformation includes both simultaneous and sequential changes in the genotype of a recipient cell mediated by the introduction of DNA corresponding to either unlinked or linked genes
Dihydrofolate Reductase (DHFR)	A proteinaceous material which acts as an enzyme and when present in increased concentrations allows eucaryotic cells to survive in the presence of increased concentrations of methotrexate

Eucaryotic Cell	A cell of an organism classified under the Superkingdom Eucaryotes including organisms of the Plant and Animal kingdoms, characterized by true nuclei formed by nuclear envelopes and by meiosis, including both a wild-type and a mutant cell
Foreign DNA I	A polynucleotide that is inserted into the eucaryotic cell
Gene Associated with Drug Resistance	A gene which encodes a protein that, when expressed at some level or concentration, allows eucaryotic cells expressing the gene to survive or proliferate in the presence of a chemical compound, such as a drug, which would otherwise kill the cells
Incorporated	Stably integrated into the chromosomal DNA within the nucleus of a cotransformed or transformed eucaryotic cell
Linked	Physically and chemically joining DNA I and DNA II into the same piece of contiguous DNA prior to their insertion into the eucaryotic cell Mammalian Cell Any cell of mammalian origin, including both a wild-type and a mutant cell
Methotrexate	A folate analog that is lethal to cells
Multiplicity	Multiple
Phenotype	An observable property of an organism or a cell as produced by the genotype in conjunction with the environment
Selectable Phenotype	A phenotype which confers upon an organism or a cell the ability to exist under conditions which kill off all organisms or cells not possessing the phenotype. Examples include drug resistance or the ability to synthesize some molecule necessary to cell metabolism in a given growth medium. Selectable phenotypes also include identifiable phenotypes such as the production of materials which pass from or are secreted by the cell and can be detected as new phenotypes either by functional, immunologic or biochemical assays
Substantially Purified	Purified to a substantial degree
Transformed Eucaryotic Cell	A eucaryotic cell which has undergone a genotypic change as a result of the introduction of DNA into the cell
Transforming	Process for changing the genotype of a recipient cell mediated by the introduction of DNA.
Unlinked	Not physically or chemically linked on the same piece of contiguous DNA

SO ORDERED.

D.Mass.,2000.
Trustees of Columbia University in City of New York v. Roche Diagnostics GmbH