The "Reverse Doctrine of Equivalents" in the World of Reverse Transcriptase

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INTRODUCTION

Although exciting legal stories are constantly making national news such stories seldom involve patent law. Until recent announcements involving a "patented mouse,"[1] patent law issues have remained essentially out of the national news (when the Supreme Court decided that living organisms could be the subject of a patent)[2]. Now that patents are back in the news I thought it might be of interest to provide some thoughts (beyond those presented by newscasters) on what was really patented. Those thoughts include an analysis of how the "reverse doctrine of equivalents" can be applied to interpreting the breadth of claims, such as the claims of U.S. patent 4,736,866 entitled "Transgenic Non-Human Mammals." (hereinafter the '866 patent). More importantly this article includes an analysis of how and why claims to living organisms should be interpreted with a greater degree of flexibility due to the ever changing dynamic nature of living systems. Upon reading this article it is hoped the reader will have a more complete understanding of (I) the "reverse doctrine of equivalents"; (II) the pioneering science involved in producing transgenic animals; and (III) the relationship between (I) and (II) in the current legal and technical environment.

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1 U.S. Patent 4,736,866 issued April 12, 1988 to *Leder et al*, entitled "Transgenic Non-Human Mammals."

2 *Diamond v. Chakrabarty*, 206 USPQ 193 (1980).

I. The Reverse Doctrine of Equivalents

Graver Tank[3] is generally considered to be the landmark case on the "doctrine of equivalents" which a patentee may invoke in the absence of literal infringement "if it performs substantially the same function in the same way to obtain the same results."[4] Surprisingly, *Graver Tank* is also a landmark case regarding the "reverse doctrine of equivalents" holding that "where a device is so far changed in principle from a patented article that it performs the same or a similar function in a substantially different way, but nevertheless falls within the literal words of the claim, the doctrine of equivalents may be used to restrict the claim and defeat the patentee's action for infringement."[5] i.e., the doctrine of equivalents can operate in reverse. The "reverse doctrine of equivalents" (hereinafter RDE) can limit claim breadth to defeat infringement or to avoid prior art and uphold validity. Thus the RDE, like the "doctrine of equivalents" can operate to the advantage or disadvantage of the patentee.[6]

Simply stated, the RDE requires reading into a patent claim, limitations which are not literally in the claim in order to give the claim a more narrowed interpretation. The RDE is not generally applied by the Patent Office perhaps because claims can be easily amended[7] while pending. The Patent Office will give claims their broadest possible interpretation[8] in order to reject the claims as

3 *Graver Tank & Mfg. Co. Inc. v. Linde Air Products Co.*, 85 USPQ 328 (1950). See also Hantman, R.D. "Doctrine of Equivalents." J. Pat. & Tm. Office Soc'y 511, (August 1988). Although *Graver Tank* is most often referred to as the landmark case on the doctrine of equivalents it was decided long after *Westinghouse v. Boyden Power Brake Co.*, 1970 U.S. 537 (1898) which laid down this rule of law.

4 See *Graver Tank* cited in note 3 at 330.

5 id.

6 Pigott, C.F., *Equivalents in Reverse*, 48 J. Pat. & Tm. Office Soc'y 291 (May 1966). The Pigott article is an extremely comprehensive article citing numerous cases as examples of how the reverse doctrine of equivalents has been applied. More recent cases than those cited by Pigott are cited later in this recent case (which refers to the 19th century case cited in note 3 above) which applies the doctrine of equivalence in reverse to limit claim breadth see *Leesona Corp. v. United States*, 185 USPQ 156, 163, U.S. Ct. of Cl. (1975), holding "It is well settled that more than a literal response to the terms of the claims must be shown to make out a case for infringement. *Westinghouse v. Boyden Power Brake Co.*, 170 US 537, 568 (1898); *Marvin Glass & Associates v. Sears, Roebuck & Co.*, 448 F. 2d. 60, 171 USPQ 263 (5th Cir. 1971); *Autogiro Co. v. United States*, 181 Ct. Cl. 55, 384 F. 2d. 391, 155 USPQ 697 (1967), rehearing denied 184 Ct. Cl. 801 (1968)."

7 37 CFR 1.115.

8 *In re Soderquist*, 140 USPQ 387 CCPA (1964); *In re Tibbals*, 137 USPQ 565 CCPA (1963); *In re Lundberg & Zuschlag*, 113 USPQ 530, CCPA (1957).

anticipated[9] by the prior art and/or unsupported by the disclosure.[10] The validity of the Patent Office's position, especially as applied to rapidly growing areas of technology, has been discussed elsewhere[11] and is outside of the scope of this article. This article will deal with the interpretation of claims by federal courts and more specifically the need for greater flexibility in interpreting claims to living organisms via the application of the RDE to narrow the scope of claims and the doctrine of equivalents to broaden their scope.[12] Such interpretation involves deciding "equivalents" and "non-equivalents" of elements recited in the claim.

When elements of the prior art or a potentially infringing device are found to be "non-equivalent" to elements of claims such a finding involves the application of the RDE. The RDE is applied by federal courts relatively frequently although it is not generally referred to *in hoc verbis* as the RDE when applied. There are four basic outcomes from cases where the application of the RDE has been argued, as follows:

1. A) Claims not narrowed by the RDE and held invalid when claims would have been infringed if valid;
   B) Claims not narrowed by the RDE and held invalid when claims would not have been infringed if valid;
2. A) Claims narrowed by the RDE and held valid but not infringed; and
   B) Claims narrowed by the RDE and held valid and infringed.

Outcomes (1A) and (1B) above can be combined for a discussion of the legal issues involved in that both result in a holding of the

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9 35 USC Section 102.

10 35 USC Section 112.

11 Winner, E.P. *Enablement in Rapidly Developing Arts-Biotechnology* 70 J. Pat. & Tm. Office Soc'y 608 (Sept, 1988).

12 With respect to the difference between interpreting a claim during prosecution before the U.S. Patent Office as opposed to interpreting a claim of an issued patent in Federal Court the former CCPA held:

> It is true, of course, that where the validity of a claim which has been granted is questioned, (and in some classes of cases) it frequently becomes proper to interpret the claim by looking to the specification, but where one seeks a patent, the statute very definitely requires that he shall particularly point out and distinctly claim that which he claims to be his invention or discovery. (See *In re Jolly*, 80 USPQ 504, CCPA (1949).

It is of course possible to interpret claims and issue a holding on validity and infringement based only on the wording of the claims, i.e. without looking to the specification for interpretation and without considering the application of either the doctrine of equivalents or the RDE. In practice however, it is all but certain that not only the specification, but the file history and the prior art will be considered to interpret claim language.

claims as invalid as anticipated and therefore not infringed. However, (2A) and (2B) provide not only separate outcomes but distinct legal reasoning behind each in that different considerations are made regarding the decision to narrow a claim's scope to avoid prior art and hold the claims valid than are applied to narrow the claims so as to result in a holding of non-infringement.

(1A & 1B) RDE not Applied—Claims Invalid

When a court holds that the RDE does not apply and the claims are anticipated and invalid the reasoning is generally straight forward—the patentee made his bed and will now be forced to lie in it. Judge Learned Hand put it another way holding that the patentee "...could not have regarded it as an important, feature; and we find no reason to use the stone which he rejected as the head of the corner."[13] All practitioners know that they run the risk of reading on the prior art by claiming broadly. This risk is balanced against the benefit of the broader property rights acquired when broader claims are obtained and found enforceable. The less ambiguous the claim the less likely a court will apply the RDE to narrow the claim and avoid prior art. Further, the greater the evidence that the patentee claimed exactly what he intended to claim the less likely the court will narrowly interpret the claim and save it from a holding of invalidity.

When a claim element is arguably ambiguous and a court refuses to use the RDE to narrowly interpret the element and save the claim from a holding of invalidity, the question arises as to whether the patentee is being unduly penalized for having a claim which is too broad when the same court would never have allowed such a broad interpretation for infringement purposes. Stated differently, the *question arises as to whether the claims are being given an inequitable pseudo-interpretation which conveniently finds the claims invalid over art when such claims would not be held to encompass infringing articles identical to those disclosed by the art.* A well established truism of the patent law holds that "That which infringes, if later would anticipate if earlier."[14] The corollary to this truism states that "... if a device does not infringe, if earlier, it would not anticipate."[15]

13 *Haseltine Corporation v. Abrams*, 27 USPQ 67 2nd Cir. (1935).
14 *Charles Peckat v. Jacobs*, 84 USPQ 4 7th Cir. (1949).
15 id

(2A) RDE Applied—Claims Valid but not Infringed

Perhaps the recognition of such pseudo-interpretations causes courts to apply the RDE and limit the interpretation of arguably ambiguous claim elements in order to save the claim from a holding of anticipation. Judge Hand was quoted above for a holding which refused to apply the RDE to limit claim breadth. However, in a different case[16] Judge Hand applied the RDE to limit claim breadth and hold overly broad and functional claims valid but uninfringed as narrowly interpreted. Judge Hand reasoned that perhaps "... someone may find valuable what was really new ..."[17] in the patentee's disclosure and "If so, perhaps the claims may be so limited as to cover such an infringer."[18] Accordingly, when a court sees subject matter which appears patentable and of potential value the court may apply the RDE to hold the claim valid and as such not apply the harsh punishment of invalidation to the patentee for claiming too broadly. However, a lesser sanction via a holding of non-infringement is rendered by applying the RDE and narrowing the claim's scope to include only what the court regards as the patentee's invention. Such holdings appear equitable in that if a claim element was arguably ambiguous the patentee could arguably not know the claim might read on the prior art and the accused infringer could arguably not know his products might infringe.

(2B) RDE Applied—Claims Valid and Infringed

In applying the RDE a court will not read into the claim elements which are clearly not recited in the claim. However, the RDE can be applied to provide narrow interpretations of elements broadly claimed. In the words of the court "To import this limitation into the claim is not to bring in an additional element. It is only to interpret with the aid of the specification one of the words of the claims so that it may not be thought so broad as to be destructive."[19] Accordingly, the RDE can be applied to narrow a claim and thereby preserve the claims validity not be adding a limitation but by construing arguably ambiguous terms in a narrow manner in accordance with the specification. Such claim interpretation could be seen not as a narrowing interpretation but as an interpretation which more truly describes the

16 *Engineering & Research Corp. v. Horni Signal Corp.*, 39 USPQ 1 2nd Cir. (1938).
17 id.
18 id.
19 *Mantle Lange Co. of America v. Geo H. Bowman Co.*, 11 USPQ 127 6th Cir. (1931).

invention for which the patent was granted. When a narrowed interpretation does not encompass the prior art but reads on products of an accused infringer a holding of validity and infringement would appear equitable.

Having described the basics of the RDE and some of the reasoning behind a court's decision to apply the RDE in different situations, let's move on to a description of a specific claim and technology which might be particularly amenable to interpretation via the application of the RDE.

II. U.S. PATENT 4,736,866 "TRANSGENIC NON-HUMAN MAMMALS"

Issued U.S. patent 4,736,866[20] (the '866 patent) is a pioneering patent for a number of reasons. Firstly, the '866 patent is the first issued U.S. patent claiming a mammal *per se*.[21] Secondly, the general technological area (i.e. transgenic animals) is at the forefront of modern science and has attracted the attention of not only brilliant scientific minds but the general public.[22] Lastly, the inventors Phillip Leder and Timothy Stewart are world renowned for their work in this quickly developing area of technology.[23] In that pioneering patents are more likely to include broad terminology which is not yet well defined, the claims of such patents are more likely to include arguably ambiguous terms which might be interpreted by an application of the RDE. Accordingly, since the '866 patent is (1) generally seen as a pioneering patent and (2) has recently attracted great interest, it was chosen for close examination.

The broadest claim of the '866 patent reads as follows:

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20 See not 1 supra.

21 *Ex parte Allen*, 2 USPQ 2d 1425, (Bd. App. & Int. 1987) indicated that multicellular animals were considered patentable by the U.S. Patent Office under 35 USC Section 101. However, no patent was issued in that case due to the prior art rejection and 35 USC Section 103.

22 Raines, L., "The Mouse That Roared" Issues in Science and Technology, Vol. IV, No. 4, p 64 (1988).

23 Philip Leder is the Chairman of the Department of Genetics at Harvard Medical School in Boston, Mass. Both Leder and Co-inventor Timothy Stewart have published extensively (see Stewart et. al. (1982) Science Vol. 217, p 1046) and are widely known and highly respected in the scientific community, their reputations having been well established apart from any work concerning the '866 patent or transgenic animals. They are particularly noted for their work with oncogenes. Note that Philip Leder participated in an Examiner interview and submitted declarations during the prosecution of the application resulting in the '866 patent.

A transgenic non-human mammal all of whose germ cells and somatic cells contain a recombinant activated oncogene sequence introduced into said mammal, or an ancestor of said mammal, at an embryonic stage.[24]

The '866 patent lists a number of known viral and cellular oncogenes and defines an "activated oncogene sequence" as an oncogene[25] which, "when incorporated into the genome of the animal, increases the probability of the development of neoplasms (particularly malignant tumor) in the animal."[26] The patent states that "[a]ny oncogene or effective sequence thereof can be used to produce the transgenic mice of the invention."[27]

In accordance with the '866 disclosure an appropriate oncogene is chosen and fused[28] to a promoter sequence[29] which serves to promote the expression of the oncogene, i.e. "turn the oncogene on." The fusion construct (oncogene connected to promoter sequence) is then cloned,[30] i.e. multiple copies of the construct are produced. Multiple copies of the cloned fusion construct are then microinjected into the pronucleus[31] of a fertilized mouse egg. The injected egg is implanted in a foster mother where the egg is allowed to grow to term to produce offspring, i.e. the egg gestates in the foster mother who gives birth to transgenic mice. Steps in producing the transgenic

24 See note 1 supra at column 9, line 35—column 10, line 2. On its face the claim is not limited to any variety of mammal (excluding only the human species) and as such would appear to cover more than the transgenic mice actually reduced to practice.

25 Simply speaking an oncogene is a gene (i.e. a unit of hereditary function generally comprised of DNA) which when expressed results in oncogenises or neoplastic growth (i.e. the development of a malignant tumor). Although much has been written about what oncogenes are and their role in neoplastic growth, much remains unknown.

26 See note 1 supra at column 1, lines 39–42.

27 id. at column 2, lines 15–16.

28 Pieces of genetic material can be fused or ligated together via a phosphodiester bond. An enzyme called T4 lipase is often used in such experiments to join fragments to each other.

29 In order for the oncogene to be expressed (cause malignant growth) the oncogene must first be transcribed—a process which allows for the production of an RNA copy of DNA of the oncogene to be produced. In order to achieve transcription a promoter sequence or DNA region must be located upstream of the oncogene in order to bind RNA polymerase—an enzyme needed for transcription. The promoter also directs the RNA polymerase with respect to where the transcription should begin.

30 Cloning involves fusing the fusion construct to yet a larger piece of DNA which is capable of self replication in an organism. The large piece of DNA with the fusion construct insert is placed in a suitable microorganism and grown. The microorganism and the fusion construct therein will replicate and multiple copies of the "cloned" fusion construct can be extracted and isolated. See Maniatis et. al. (1982) Molecular Cloning A Laboratory Manual (Cold Spring Harbor Laboratory).

31 The male nucleus of the fertilized egg is used due to its larger size.

mouse are schematically outlined below in Figure 1.[32] The first generation offspring shown in Figure 1 are the transgenic mice. These mice contain the fusion construct (promoter sequence fused to oncogene) in all their cells. Since the fusion construct is in the germ cells (i.e. the sex cells) of these transgenic mice, these mice can be bred with each other to consistently produce offspring which will also contain the fusion construct in all of their cells.

The claims of the '866 patent specifically indicate that the oncogene sequence is "introduced into said mammal, or an ancestor of said mammal, at an embryonic stage." (see claim 1 above). The disclosure specifically teaches "introduction" by microinjection into the pronucleus of a fertilized egg in the manner shown in Figure 1 above. The term "introduced" is at least arguably ambiguous as many terms covering pioneering inventions are. Accordingly, the question arises as to whether the RDE would be applied to interpret the claims of the '866 patent. More specifically, the question arises as to whether the RDE would apply to narrow the scope of the claims if the oncogene is "introduced" via a method not disclosed in the specification which resulted in a "mammal all of whose germ cells and somatic cells contain a recombinant activated oncogene sequence." (see claim 1 above). The patentees might argue in favor of a literal reading and interpretation of the claims in order to attack an infringer whereas an infringer might argue the RDE applies so as to limit the claim breadth only to mammals wherein the introduction of the oncogene was via the microinjection method disclosed. Conversely, the patentee might be forced to argue in favor of applying the RDE to limit claim breadth when faced with prior art disclosing transgenic mammals of the type claimed wherein such transgenic mammals had oncogenes "introduced" in a manner not disclosed in the specification.

Reverse Equivalents of the Mouse Covered by the '866 Patent

Alternative methods (not disclosed in the '866 patent) of introducing an oncogene to all the cells of an embryonic mammal will now be presented. The presentation will provide a reference point for

32 For a basic description of the technology involved with producing transgenic animals see Watson et al., Recombinant more detailed description can be found in Gorden et. al., Genetic Transformation of mouse embryos by microinjection of purified DNA, Proc. Natl. Acad. Sci. U.S.A. Vol. 77 No. 12 pp 7380–7384, December 1980 and also Wagner et. al., Proc. Natl. Acad. Sci. U.S.A. Vol. 78, pp 5016 (1981).

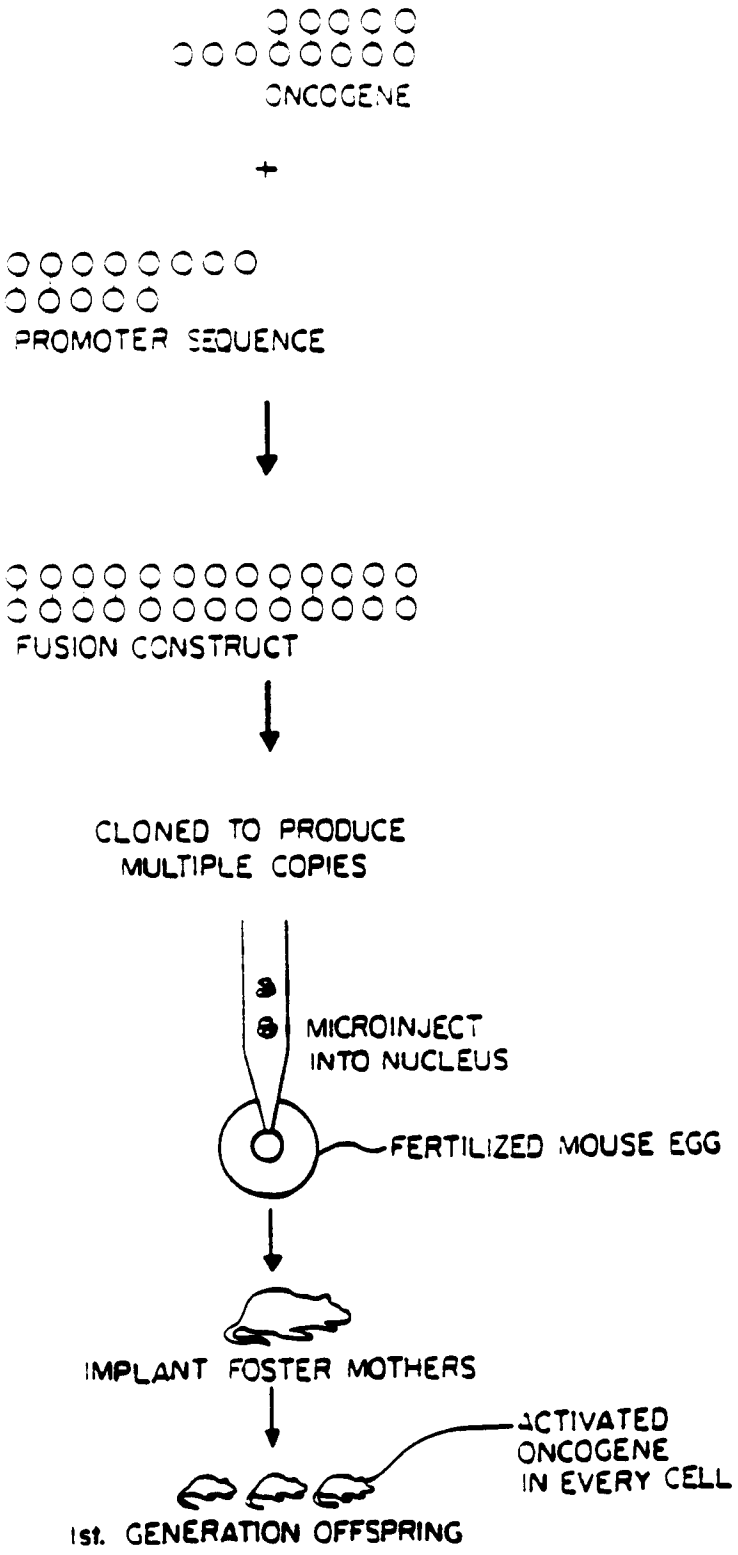
ONCOGENE
+
PROMOTER SEQUENCE
FUSION CONSTRUCT
CLONED TO PRODUCE
MULTIPLE COPIES
MICROINJECT
INTO NUCLEUS
FERTILIZED MOUSE EGG
IMPLANT FOSTER MOTHERS
ACTIVATED
ONCOGENE
IN EVERY CELL
1st. GENERATION OFFSPRING

Fig. 1

an analysis of how the RDE might apply to interpreting the claims of the '866 patent. It should be noted that any alternative methods of introducing oncogenes (methods not disclosed in the specification but potentially capable of producing mammals encompassed by the claims of the '866 patent) might be used by a potential infringer or, alternatively taught by a prior art disclosure.

The oncogene could be introduced by microinjection techniques not taught in the '866 patent[33] and could also be introduced in a manner not involving microinjection. Present recombinant technology makes it possible to "package" a fragment of genetic material such as an oncogene in a virus.[34] Once "packaged" the natural infectious ability[35] of the virus is used (as shown below in Figure 2) by placing the virus in contact with (1) a cell (e.g. a fertilized egg cell); (2) a group of cells; or (3) an embryo and allowing the virus to infect the cell or cells with the "packaged" genetic material. A schematic representation of how a virus could be used to introduce an oncogene to a mammal at an embryonic stage to provide a mammal "all of

33 The oncogene can be introduced by microinjecting the DNA into the fertilized egg at a different place and/or time than that specifically disclosed in the '866 patent. For example, the oncogene could be microinjected into (1) the female nucleus, (2) the cytoplasm, (3) the female nucleus and the cytoplasm or (4–6) into the pronucleus in combination with, any of (1)–(3), i.e. injected into two or three places in the egg. Further, any of (1)–(6) might be carried out at a stage of development not specifically taught by the '866 patent, i.e. a stage of development beyond the single cell fertilized egg stage, e.g. 2 cell stage, 4 cell stage, etc.

34 A virus is a protein coat surrounding a core of genetic material capable of growth and multiplication only in living cells. The type of virus being referred to here is a eukaryotic RNA retrovirus which can integrate a DNA copy of their genome into a chromosome of a host cell such as the fertilized egg cell.

35 The virus attaches itself to a host cell and injects its RNA genome into the host. A viral enzyme called RNA dependent DNA polymerase or reverse transcriptase synthesises a DNA copy from the RNA template. The DNA copies have long terminal direct repeat sequences which allow the DNA to integrate into the host's DNA in a transposon-like manner.

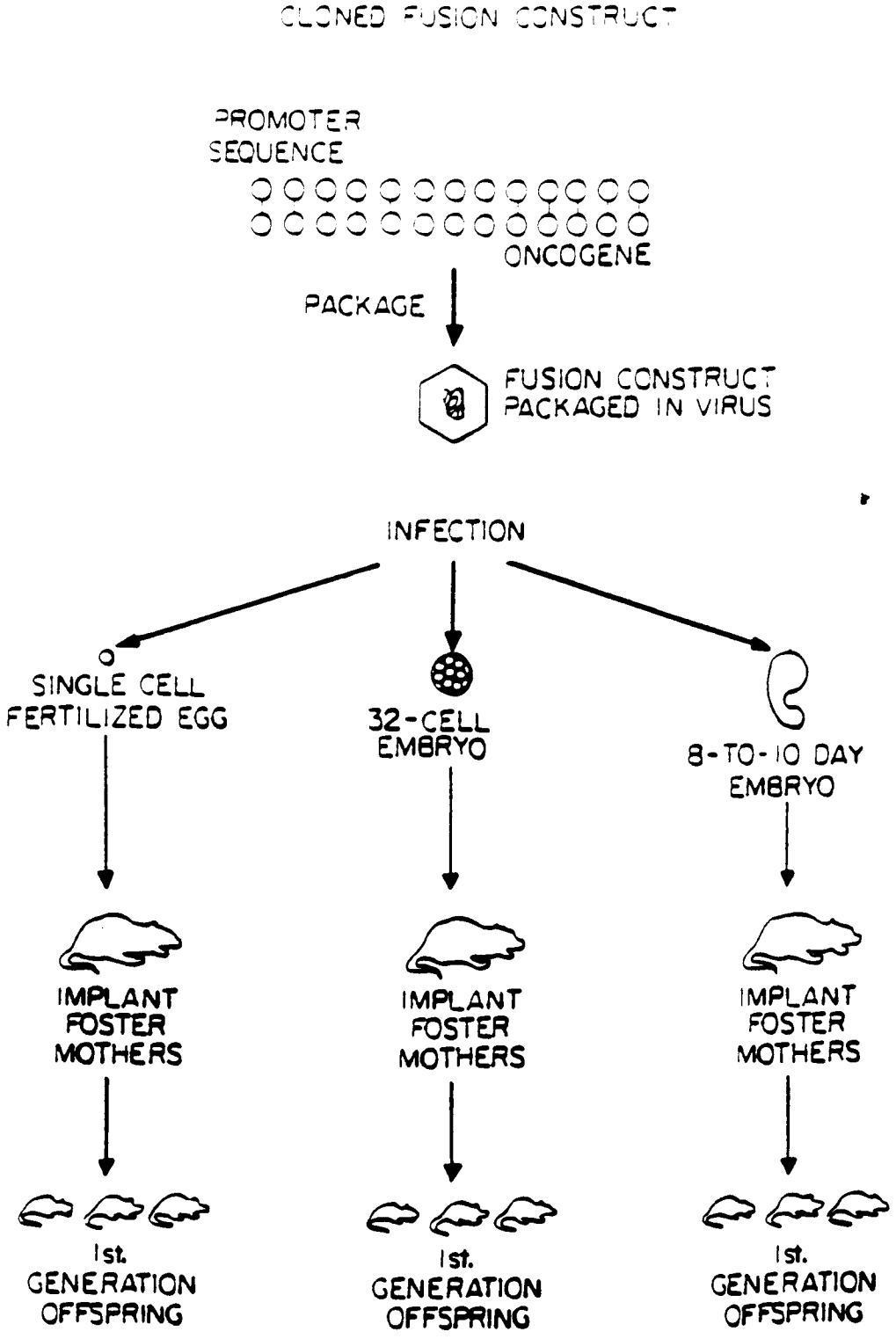
CLONED FUSION CONSTRUCT
PROMOTER SEQUENCE
ONCOGENE
PACKAGE
FUSION CONSTRUCT PACKAGED IN VIRUS
INFECTION
SINGLE CELL FERTILIZED EGG
32-CELL EMBRYO
8-TO-10 DAY EMBRYO
IMPLANT FOSTER MOTHERS
IMPLANT FOSTER MOTHERS
IMPLANT FOSTER MOTHERS
1st. GENERATION OFFSPRING
1st. GENERATION OFFSPRING
1st. GENERATION OFFSPRING

Fig. 2

whose germ cells and somatic cells contain a recombinant activated oncogene sequence" is shown below in Figure 2.[36]

The genetic material (oncogene plus promoter sequence) introduced to the fertilized egg cell by microinjection (as shown in figure one and described in the '866 patent) is in the form of deoxyribonucleic acid[37] (hereinafter DNA). Once introduced the DNA is copied along with all the DNA of the cell in a reaction initiated by DNA polymerase.[38] However, a retrovirus of the type which might be used in accordance with the method shown in figure 2 has ribonucleic acid[39] (hereinafter RNA) as its genetic material. The RNA is introduced to the cell by the virus and a DNA copy of the RNA is produced by a viral enzyme called "RNA—dependent DNA polymerase" or "reverse transcriptase."[40] The enzyme is appropriately referred to as "reverse transcriptase" in that it catalyzes the synthesis of DNA from an RNA template while the more well known enzyme "transcriptase" and "reverse transcriptase" are shown schematically below.

36 Figure 2 is a partial adaptation of a figure shown in Watson et al., Recombinate DNA—A Short Course, Scientific American Books, N.Y. 1983. Further details of such can be found in Jahner et. al., De Novo Methylation and Expression of Retroviral genomes during mouse embryogenesis, Nature, Vol. 298, p 623, August 1982. See also Reynolds et. al., on Activated Oncogenes in B6C3FI Mouse Liver Tumors:Implications for Risk Assessment, Science, Vol. 237, p 1309, September 11, 1987. Each of the methods shown in Figure 2 is clearly quite different from the microinjection technique of Figure 1 and the '866 patent. It is also interesting to note that the different times of infection shown in the three procedures of Figure 2 yield very different results, one from the other. Summarizing and over simplifying the results of the three procedures it can be said that (1) introduction at the single cell stage may result in integration of a large number of oncongenes into all cells with the genes being highly methylated (methylation is believed to prevent expression) if introduced to the pronucleus where introduction to the cytoplasm resulted in single copies of the gene in all cells with about 10% of the cells producing mRNA of that gene (mRNA is an indication of expression); (2) introduction at the 32 cell stage resulted in integration of the oncogene into some cells of a few tissues with a high degree of methylation of the oncogene; and (3) introduction at the 8 to 10 day embryo stage resulted in integration of the oncogene into all tissue with the gene being unmethylated and highly expressed. Such experiments demonstrated the effect of cell differentiation.

37 DNA or deoxribonucleic acid is the basic genetic material of all living organisms, but see note 39 infra. It is generally double stranded and the strands run in opposite directions and are coiled around in a double helix. Purine bases on one strand from hydrogen bonds with corresponding pyrimidine basis on the other strand.

38 DNA polymerase is an enzyme which synthesises DNA by moving along a template strand in the 5' to 3' direction and successively adding nucleotides to the free 3' hydroxyl group of the growing strand. There are three types of DNA polymerase and DNA polymerase III is the type referred to here.

39 In some organisms RNA or ribonucleic acid chains are the source of genetic information and not DNA. (See note 36 supra). The RNA can be in a single stranded or double stranded form.

40 Reverse transcriptase or RNA-dependent DNA polymerase is an enzyme present in the protein coating of a virus (see note 33 supra) which catalyzes the production of a DNA copy from an RNA template when primed with a specific oligodeoxyribonucleotide.

transcriptase
DNA template ⟶ RNA

DNA ⟵ RNA template
reverse
transcriptase

The method shown in Figure 1 and described in the '866 patent could produce a mammal encompassed by claim 1 of that patent. However, the methods shown in Figure 2 could also result in producing a mammal onto which claim 1 would literally read. Since claim 1 would read literally onto a mammal produced by a method of Figure 2 the doctrine of equivalents need not be applied to show infringement. However, as pointed out above, the term "introduced" is at least arguably ambiguous. Accordingly, the question arises as to whether the RDE would apply to restrict the breadth of the term "introduced" and thereby restrict the scope of the claims of the '866 patent so that they would not be infringed by transgenic mice produced in accordance with the methods shown in Figure 2.

III. The Current Legal and Technical Environment

It is well settled in chemical patent law that a claim to a compound *per se* encompasses all compounds covered by the claim regardless of how the compound is made.[41] Applying current chemical patent law to the claims of the '866 patent (provided such claims are viewed as compound claims) would initially result in finding that mammals produced by the methods shown in figure 2 infringed those claims. However, any claim to an animal would require the use of terminology which is at least in part functional in that the living system is itself functional. The claims of the '866 patent include functional terminology by using the word "introduced". Further, the claims of the '866 patent are to a living system which is constantly changing, e.g. growing, developing tumors, aging. Other terms of the '866 patent claims such as "activated oncogene sequence" are

41 This basic concept has been accepted in the interpretation of chemical claims for a considerable period of time. Because compound claims are interpreted to cover the compound regardless of its method of production, such claims are generally considered more desirable than process claims. "[T]he claim is not restricted to the product made by the described process, but covers the chemical individual, however produced." *Mauer v. Dickerson*, 113 F. 870,874 (3d. Cir. 1902).

functional by any definition including the definition provided by the '866 patent. These facts combine to raise the question as to whether it is possible to have a true animal *per se* claim i.e. a claim which does not include functional process type terminology. When animal *per se* claims are viewed in this manner, i.e. as process or product-by-process type claims, the claim elements may be interpreted as functional elements which are arguably ambiguous and as such subject to narrowed interpretations under the RDE.

It is recalled from the early discussion of *Graver* that the RDE applies "where a device is so far changed in principle from a patented article that it performs the same or a similar function in a substantially different way."[42] With regard to the situation at hand the "device" is a living organism and the first step toward achieving the desired final result (providing a transgenic mammal with an oncogene in all its cells) is clearly achieved in a "substantially different way."[43]

Regardless of whether transgenic mammals are produced by the means shown in Figure 1 or those suggested in Figure 2, man's ability to influence the final results ends after the introduction of the genetic material. The DNA introduced by microinjection (as shown above in Figure 1) is copied via DNA transcriptase while the RNA of the virus (as shown above in Figure 2) is copied via reverse transcriptase to provide a DNA copy. The transgenic mammal produced by either means (microinjection or viral infection) produces the final product (a mammal with an oncogene in every cell) in a substantially different way. The "different way" being referred to here is not a comparison of the microinjection (Figure 1) versus viral infection (Figure 2) methologies but rather a difference in what the biochemistry of the organisms is initially doing to achieve integration of the foreign genetic material into the genome of all the cells of the organism which is eventually born. More specifically, the "different way" is believed to be a "substantially different way" due to the way transcriptase as opposed to reverse transcriptase, operate in the organism. The term "introduced" is arguably ambiguous for a number of reasons. Firstly, the introduction might mean the infusion of the oncogene into the mammal via microinjection or other means as per Figure 2, or secondly, the introduction might mean the integration of the oncogene into the genome of the mammal. Such integration is essential to the production of a transgenic mammal and may occur via the action of

42 See note 3 supra. The quote here represents the basic criteria for applying the RDE.
43 id.

transcriptase (Figure 1) or reverse transcriptase (Figure 2). Having established an argument for the presence of a potentially ambiguous term in the claims of the '866 patent it can be argued that the RDE should apply to narrow the interpretation of the term "introducted". Since, the ambiguity may not have been recognized by the patentee or an accused infringer, equities would require restricting claim breadth to hold the claims valid over piror art showing the transgenic animals of Figure 2 while not encompassing those transgenic animals for purposes of infringement. Such a holding would be consistent with the truism "...if a device does not infringe, if earlier, it would not anticipate."

Chemical Reactions Versus Cellular Differentiation

Different chemical reactants can react via different mechanisms to achieve the same final product. That final product might well be covered by a compound *per se* claim irrespective of how the compound was synthesized. By analogy any mammal with an activated oncogene in every cell might well be covered by the claims of the '866 patent irrespective of how the mammal was produced. Such a holding would not be consistent with the narrowed interpretation of the '866 claims given above. Accordingly, some logical explanation must be provided as why claims to living organisms are more subject to interpretation via the RDE than are claims to chemical compounds. I believe that explanation lies in the every changing dynamic nature of living organisms.

The methods of introducing an oncogene to a mouse genome suggested in Figure 2 are not merely theoretical possibilities presented for the mere purpose of discussion. Such methods have been carried out[44] and the results obtained demonstrate the unpredictability[45] of applying such methodologies to living organisms. More specifically, the results show that the degree of expression[46] of the oncogenes introduced (i.e. the ability of the oncogenes to later cause malignant tumors) is very dependent on the time at which the oncogene is

44 See note 36 supra and Jahner et. al. De Novo methylation and expression of retroviral genomes during mouse embryogenesis, Nature, Vol. 298, p. 623 August 12, 1982. See also Watson et. al. cited in note 22 and articles cited therein.

45 See note 36 supra. The occurrences of cell differentiation are so complex that the ability to obtain integration let alone express of newly introduced genetic material is highly unpredictable.

46 Even if genetic material is introduced to an organism and is integrated into the genome of that organism the material may well remain unexpressed. To obtain expression the gene must be "read" or transcribed to mRNA which must then be translated to a protein. In the case of an oncogene observable expression is in the form of a tumor growth.

introduced to the embryo. More specifically, as the fertilized egg divides and grows, each division provides a new set of cells with capabilities different in some ways from the cell or cells from which they come. Such different cellular capabilities determine whether and to what degree the oncogenes introduced to the living system will be expressed. A strict inflexible interpretation of the claims of the '866 patent would not provide any true appreciation of the changes which continually take place in all living systems. The changing cellular capabilities which take place from the single cell egg to adult animal is referred to generally as "cellular differentiation."[47] It is the continuing phenomenon of cell differentiation resulting in a dynamic changing system which I believe requires that claims defining the boundaries of pioneering inventions directed to living organisms be more carefully written and more flexibly construed via the application of the RDE than claims defining mere chemical compositions or reactions.

Analogies are often drawn between real property (land) and intellectual property (invention). It is pointed out that those with the daring, skills and abilities to first discover a new area of land (property) are entitled to claim it broadly in that they were the first to show the way to the previously unknown, i.e. true pioneers. The analogy between property rights in land and property rights in inventions works well when the inventions are mechanical (i.e. static and predictable in their nature). However, the analogy breaks down as the degree of unpredicatability of the invention increases. Because chemicals do not react or interact with the same degree of predictability as gears and levers, numerous chemical examples must often be given to demonstrate the predictability of the chemistry within the boundaries claimed. The degree of unpredictabilty is dramatically increased with living as opposed to mere chemical systems. However, more importantly a living system is not only complex and unpredictable but dynamic, moving, continually changing, i.e. "living". The continually changing character of living systems allows for descriptions, or claims defining such living systems to be accurate only for a given point in time. As time passes a living system changes and so must any boundaries defining the outer limits of that system.

47 Cellular differentiation is the biological phenomenon whereby one cell becomes different from another. The study of this phenomenon is perhaps the most interesting and complex field of modern science. An understanding of the details of how and why cells become different over time would provide an understanding of the miracle of life itself.

Thus any changing boundaries defining a living system are substantially non-analogous to the fixed boundary lines defining real property or the claims which define "static" or non-living intellectual property. The application of the RDE and/or the doctrine of equivalents in interpreting claims to living systems provides the degree of flexibility required to accurately claim such living systems over time.

Current Cases on RDE

The CAFC refers to the RDE in the *Texas Instruments v. International Trade Commission*.[48] (hereinafter *TI v. ITC*) case which also dealt with claim interpretation for a "pioneer" invention. Since the '866 patent could well be classified as a "pioneer" invention and since its claims would appear to be subject to interpretation under the RDE the *TI v. ITC* case is particularly relevant to the issues at hand, i.e. how would current law be applied to construe the property rights claimed in the '866 patent.

In *TI v. ITC* the CAFC refers to a Supreme Court decision which characterized a pioneering invention as "a distinct step in the progress of the art, distinguished from a mere improvement or perfection of what had gone before.[49] The CAFC recognized that such a statement is hardly definitive on the issue of what is a "pioneer" invention and states "There is not a discontinuous transition from mere improvement to pioneer."[50] In view of such the CAFC held:

> The judicially "liberal" view of both claim interpretation and equivalency accorded a "pioneer" invention, *see Morley Sewing Machine Co. v. Lancaster, 129 U.S. 263 (1889)*, is not a manifestation of a different legal standard based on an abstract legal concept denominated "pioneer." Rather, the "liberal" view flows directly from the relative sparseness of prior art in nascent fields of technology.[51]

Thus, it would seem that: (1) the more crowded the art the less likely the invention will be held to be a "pioneer" invention and (2) the closer the claims are to "touching" the prior art the less likely the invention is a "pioneer" invention. When writing claims to a large expanse of virgin territory (land) or to an invention in a nascent

48 *Texas Instruments v. ITC*, 6 USPQ 2d 1886. CAFC (1988). In another recent case a federal court applied the RDE and held "Thus, based on the reverse doctrine of equivalents, defendants are entitled to summary judgement as to all three patents." *Precision Metal v. Jetstream Systems*. 6 USPQ 2d. 1704, 1708 N.D. CA. (1988).

49 See *TI v. ITC* at 1888.

50 id.

51 id.

(newly born) field of technology the pioneer can use language which would be regarded as vague and indefinite if used to describe less expansive property more closely related to property already explored or known. One must be afforded greater flexibility in describing the property rights surrounding a completely new and unexplored territory. This need for flexibility in describing a property right is significantly increased when the property right is a living, changing system. That flexibility can be afforded by the application of the "doctrine of equivalents" and the RDE. The CAFC noted this need for flexibility in *TI v. ITC* and held

> As in all cases involving assertions of equivalency, wherein the patentee seeks to apply its claims to structures not disclosed by the patentee, the court is required to exercise judgment.[52]

Graver Tank is referred to as the basis of the RDE and language from that case is quoted by the CAFC in *TI v. ITC* to describe the RDE. After quoting from *Graver Tank* the CAFC states "Indeed, it might better be called a doctrine of non-equivalents." Thus, courts have for some time recognized a need for flexibility in interpreting the property rights described by claim language. As stated in *TI v. ITC* "the court is required to exercise judgement."[53] The need to exercise judgement to determine equivalents or non-equivalents grows in proportion to the size of property being described. Although the same legal standards are applied,[54] the effects of their application is greater due to the shear size of the property right being interpreted. A one percent expansion or reduction of a description of North America has dramatically greater total gross significance than a one percent expansion or reduction of a description of a residential lot most of us might live on. Further, any initial description of North America after its discovery is much more likely to be subject to error than a description of a residential lot in a housing development.

In *TI v. ITC* the technology of interest was electronic calculators and not transgenic animals. None-the-less the legal principles applied by the court are applicable to interpreting the claims of the '866 patent. The court states that "The reverse doctrine of equivalents is invoked when claims are written more broadly than the disclosure

52 id at 1889.
53 id.
54 id at 1888. (See the quote in the text at note 51).

warrants."[55] An examination of claim 1 of the '866 patent and the patent disclosure shown schematically in Figure 1 would indicate (in view of Figure 2) that the claim could well be interpreted more broadly than the disclosure warrants. The claim covers means of "introducing" an oncogene which are not disclosed in the specification (such as the means shown in Figure 2). The court goes on to state that "The purpose of restricting the scope of such a claim is not only to avoid a holding of infringement when a court deems it appropriate but often is to preserve the validity of claims with respect to their original scope."[56]

Although the claims of the '866 patent might be described as "product" or "compound" type claims they include functional terminology. The oncogene is described as having been "introduced" to the mammal. (It must be recalled from the earlier discussion that the RDE can not be used to add a new element to the claims). The methods shown in Figure 2 "introduce" an oncogene and as such literally perform the claimed function. However, those structures (shown and described in connection with Figure 2) performing the function of introduction are not equivalent to the structures taught by the '866 patent. The structures such as the viral enzyme reverse transcriptase used to "introduce" the oncogene to the cells genome, (as shown in Figure 2) transcend the fair range of equivalents shown in the '866 patent. It would seem as though the criteria required for the application of the RDE are present and as such a court might hold that any transgenic mammals produced by the methods of Figure 2 would not infringe the claims of the '866 patent.

Conclusion

The "reverse doctrine of equivalents" and the "doctrine of equivalents" provide established mechanisms by which courts can provide flexibility to the interpretation of claim language. The two

55 See *TI v. ITC* at 1889. Also see *UMC Electronics Co. v. United States*, 228 USPQ 396, 400 U.S. Cl. Ct. (1985) which held "When all the claims of a patent read literally on a prior art reference, this court must avoid anticipation, if possible, and secure to the patentee the just fruits of his actual invention by construing those claims to cover what the drawing and specification disclose."

56 See *TI v. ITC* at 1889. See also *Chisholm-Ryder Co., Inc. v. Mecca Bros., Inc.* 217 USPQ 132 W.D. N.Y. (1983) which cites an old U.S. Supreme Court case and held—"*Westinghouse v. Boyden Power Brake Co.*, 1970 U.S. 537, 568 (1898), laid down what is now the rule of law—to wit, that, even where the claims in suit read literally on an accused device, if such device does not appropriate the principle and spirit of the patented invention, infringement is avoided. This is the application of one edge of the double-edged sword—the doctrine of equivalents."

doctrines respectively provide legal foundations for narrowing or broadening the scope of the intellectual property rights a patentee may claim as exclusively his. The magnitude of any narrowing or broadening will vary somewhat with the importance of the invention with pioneering inventions being afforded greater flexibility in the interpretation of their claims than mere improvement type inventions. Claims defining the continually changing boundaries of living systems would seem particularly amenable to the application of either or both doctrines. Arguably ambiguous terms are more likely to be present in claims directed to pioneering inventions. The effects of any ambiguity will be amplified when such a term is used to describe a continually changing, dynamic or "living system." Neither the "pioneer" status or "living" aspect of a property would require the application of completely new legal criteria to interpret claims to such property rights. However, greater flexibility must be afforded to the interpretation of claims to living organisms. A refusal to afford such flexibility would be tantamount to a refusal to recognize the tremendously unique character all living organisms process.

EPILOGUE

The title of the article refers to a legal doctrine and a biochemical catalyst which are each respectively designated as being the "reverse" of their more well known counterparts. To make a point a scenario was described whereby the operation of reverse transcriptase might require the application of the reverse doctrine of eqivalents. The symmetry of the scenario seemed to make the arguements based thereon flow well. This "forward-reverse," "positive-negative" "yin-yang"[57] symmetry applies particularly well to descriptions of problems involving living organisms but applies to any "living," "thriving" system.

The '866 patent refers to an "activated oncogene" as increasing .."the probability of the development of neoplasms"... . More recent findings indicate that neoplastic growth (i.e. cancer) may be caused not by activating an oncogene but by deactivating an anti-oncogene. (See Weinberg, R.A., "Finding the Anti-Oncogene," Scientific American, Sept. 1988). It may be that all cells would grow out of control if their growth were not suppressed by the action of anti-

57 In Chinese cosmology the "yin" is the feminine passive principle in nature and exhibits darkness, cold, and wetness. The "yang" is the masculine active principle and exhibits light, heat, and shyness. The "yin" and "yang" combine to produce all that comes to be.

oncogenes. If Weinberg is correct and his work is extrapolated on, it could be established that there is no such thing as an activated oncogene but only normal growth promoting genes which grow out of control in the presence of defective growth supressor genes, i.e. defective anti-oncogenes.

The anti-oncogenes are but another example of living systems delicately balanced by mechansims operating in opposing directions. While the system remains ever changing but balanced it thrives. Such is true of all "living" systems including legal systems. If the United States patent system established to promote the progress of science and the useful arts is to thrive it must operate under balanced mechanisms. It must be possible to apply such mechanisms to issues such as claim interpretation in a manner which allows for flexibility (expansion and restriction) in the interpretation of claim elements. Judgement must be applied to determine the degree of flexibility to be afforded. That judgement must weigh the benefits of upholding patents as enforceable against the benefits of promoting an entrepreneurial spirit to design around and go beyond a patent.