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ARTICLES

RECOMBINANT PRODUCTS AND NONOBVIOUSNESS: A TYPOLOGY*

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Developers of products obtained through recombinant DNA technology routinely seek patent protection for these products to recoup their research and development costs which are comparable to those involved in traditional medicinal chemistry. Similar to the previous experience in chemistry, the determination of obviousness for patentability appears to be a daunting issue for recombinant products such as proteins, underlying DNA code, and DNA vectors which are required for expression in recombinant organisms. This article is an attempt to make an honest and thorough analysis of obviousness in the recombinant field, taking into account the similarities and differences between traditional chemistry and recombinant technology. It argues that even though recombinant products can be considered "chemical compounds," the case law on obviousness developed for traditional chemistry cannot be applied in all cases. The significance of structural similarity between prior art and claimed compounds — so important in traditional chemistry — makes little sense in relation to recombinant products obtained by means other than molecular modification of prior art compounds. In such cases, one should apply the original meaning of 35 U.S.C. § 103,[1] rather than the rigid subtests which were devised in a different context.

This article will distinguish three categories of recombinant products including:

1. "Translation" inventions, such as naturally-occurring DNAs retrieved from the corresponding protein, where the contribution of the inventor resides in his use of techniques which enable the transformation of prior art basic information (amino acid sequence plus DNA library or database) into a specific DNA sequence. Because this approach provides a unique way to systematically make useful discoveries, this article argues that none of the obviousness analysis developed in the chemical or mechanical arts applies. Under current law, and despite the efforts of the Federal Circuit,[2] "translation" inventions are at great risk of being found obvious, as soon as the underlying technology is mature.

2. "Molecular modification" inventions, such as second-generation proteins or DNAs, obtained by incremental modifications of the sequence. The contribution of the inventor resides in the creation *de novo* of at least some part of the sequence, starting from a prior art sequence as template and substituting, adding, or subtracting

1. *See generally* 35 U.S.C. §§ 1-376 (1988).
2. *See infra* note 43.

elements (amino acids or nucleotides) having no autonomous functional meaning. Due to similarities in their mode of conception, this article argues that the obviousness analysis developed in the traditional chemical case law applies without major obstacles to recombinant "molecular modification" inventions.

3. "Combination" inventions, such as DNA vectors or second-generation proteins designed by combining functional domains. In such inventions, the contribution of the inventor resides in the new combination of prior art functional units (sequences). Due to similarities in their mode of conception, the obviousness analysis developed in mechanical inventions which combines prior art functional elements applies without major problems to recombinant "combination" inventions.

The first section of this paper is dedicated to a brief review of recombinant technology. Section two describes the statutory requirement for nonobviousness found in § 103(a) of the Patent Act. The development and current understanding of the standard of obviousness are explained first, followed by a review of the chemical case law. The third section offers a typology of recombinant inventions. This section successively describes "translation" inventions, "molecular modification" inventions, and "combination" inventions, as well as the relevant case law.

I. SCIENTIFIC BACKGROUND[3]

Recombinant technology represents the paradigm of modern biotechnology and remains its main tool. All living entities obey a "program" (not unlike a computer operating system) encoded on a universal chemical support: DNA, or deoxyribonucleic acid.[4] The basic idea of recombinant technology is to take advantage of this common denominator by placing functional units of the DNA "program" — genes — from a complex, poorly understood, expensive, or rights-bearing organism (such as man) into a simple, thoroughly studied, cheap, or rights-deprived organism (such as bacteria, yeast, cells, or non-human mammals). This approach has yielded several invaluable therapeutic products, such as Factor VIII, erythro-

3. For a general background on molecular biology, see PAUL BERG & MAXINE SINGER, DEALING WITH GENES: THE LANGUAGE OF HEREDITY (1992); JAMES D. WATSON ET AL., RECOMBINANT DNA: A SHORT COURSE (1983); JAMES D. WATSON ET AL., MOLECULAR BIOLOGY OF THE GENE (4th ed. 1987).

4. Some viruses (e.g., HIV) use RNA (ribonucleic acid), instead of DNA. RNA is chemically very close to DNA. Both are collectively known as nucleic acids.

poietin, human growth hormone, tissue plasminogen activator (t-PA), granulocyte colony-stimulating factor (G-CSF), and hepatitis B vaccine, among many others. All are mass-produced replicas of natural proteins, previously available from living organisms only in minute quantities. In addition, recombinant technology has already started to produce enhanced versions of natural proteins called second-generation proteins.

Contained in one or several chromosomes, DNA represents the chemical support for virtually all the information necessary to the living cell.[5] As such, DNA must be very stable during the life time of the living organism.[6] DNA consists of a long polymeric chain of only four chemical building blocks (bases) called adenine, thymine, guanine, and cytosine respectively abbreviated as A, T, G, and C. The order of these bases (sequence) determines the information contained in the DNA. The relevant information[7] encoded in DNA is transmitted to other informational molecules (RNA or protein). In addition, some DNA information is used (read) directly on the DNA as signals indicating the beginning and the end of functional units, or as regulatory signals for transmission of nearby information to other molecules.[8]

Downstream transmission of the information contained in DNA is done by transcription of DNA into RNA. The latter is another polymeric chain, chemically very close to DNA, which uses the same chemical building blocks, except that thymine (T) is replaced by uracil (U).[9] Most RNAs are only messengers of the information contained in DNA, hence its name messenger RNA (mRNA). They transmit the information further downstream, by translation into protein (see Figure 1). Other RNAs are directly used as effectors for various cellular tasks, such as assisting the translation of mRNA into protein (transfer RNA (tRNA) and ribosomal RNA (rRNA)).

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5. The basic functional unit of life is the cell. Organisms can be unicellular (bacterias, yeasts, protozoas, some mushrooms) or pluricellular (superior organisms). All cells composing a given pluricellular organism contain the same DNA information.

6. Variations occur either during recombination between two individuals (sexual or asexual) or accidentally (mutations).

7. In superior organisms, a great proportion of DNA (about 95% in man) does not convey information and is not transcripted into RNA. The role of this DNA, if any, is poorly understood. *See supra* note 3.

8. *See id.*

9. In addition, RNA and DNA also differ by the sugar residues attached to each base. RNA uses ribose, and DNA uses deoxyribose.

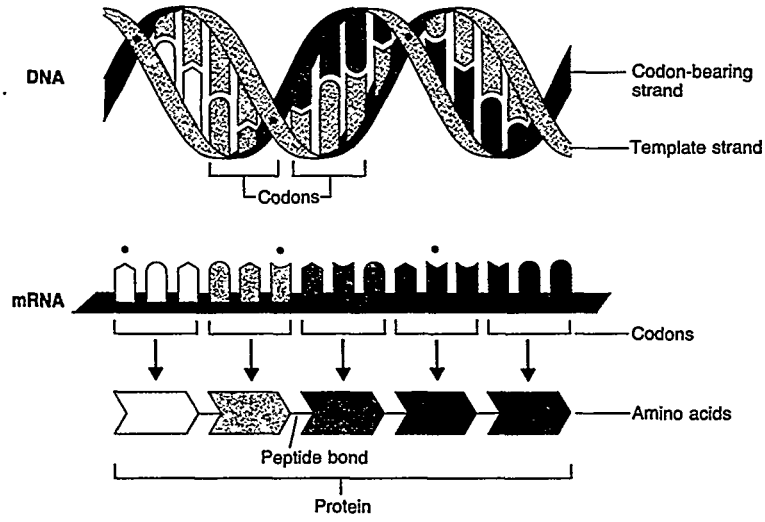

Fig. 1 Transmission of information from DNA to protein (from Paul Berg, Dealing with Genes — the Language of Heredity, University Science Books, Sausalito, California 63 (1992)).

Messenger RNAs are intended to be translated into proteins. Proteins are also polymeric chains but are chemically very different from both DNA and RNA. Whereas nucleic acids have only four bases, proteins have 20 different building blocks, called amino acids. Accordingly, the translation pattern from RNA into proteins is not as straightforward as the transcription from DNA into RNA where one base corresponds to its complementary base. This translation pattern, called genetic code, was elucidated during the 1950s and 1960s.[10] To code for as many as 20 different amino acids, the four bases of DNA and RNA have to be combined into words of at least three letters.[11] Groups of 3 bases, called codons, code for each amino acid. The number of possible codons, which can possibly be formed with a four-letter alphabet ($4^3 = 64$) exceeds the number of natural amino acids (20). As a result, most amino acids are coded by two or more codons, and the only role of several codons is to signal the end of translation.[12] This relative loss of information from DNA to protein

10. F.H.C. Crick, *The Genetic Code,* SCI. AM., Oct. 1962, at 66.

11. One-letter words of a four-letter alphabet (A, T, G, and C) would encode only 4 amino acids; whereas two-letter words would encode only 16 amino acids (4^2).

12. Codons TAA, TAG, TGA. In addition, one codon (ATG) codes for an amino acid (methionine) as well as signals the beginning of translation.

is generally referred to as the "degeneracy of the genetic code" (see Figure 2).

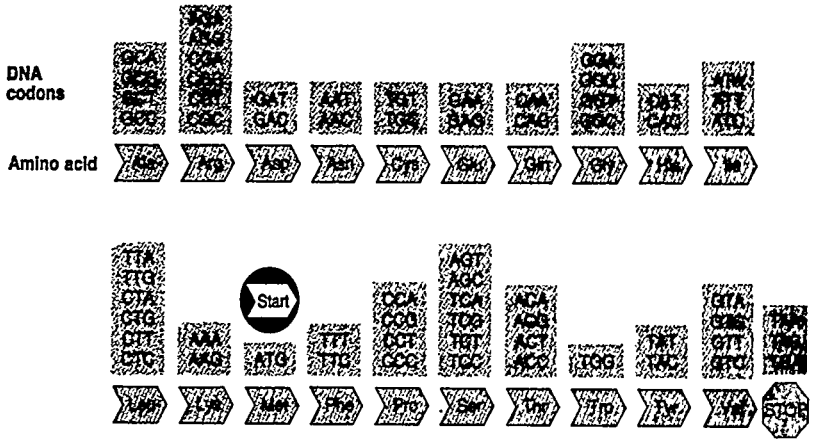

Fig. 2 The genetic code (from Paul Berg, Dealing with Genes — the Language of Heredity, University Science Books, Sausalito, California 64 (1992)).

The amino acid sequence of proteins, also called primary structure, defines their three-dimensional shape. Although the amino acid sequence is linear in itself, the specific pattern of amino acids directs the intramolecular interactions to define the ultimate molecular shape. Protein folding — called secondary structure — encompasses either a helicoidal disposition, called α-helix, or a flat disposition, called ß-sheet. Beyond these gross shapes, the protein undergoes further folding to reach its tertiary structure, approximately globular in shape. Once in its tertiary structure, a protein bears one or more "functional domains" able to interact with other molecules, thereby conferring chemical properties on the protein.

Proteins are certainly the most important effectors in living cells; their tasks are too diverse to enumerate. This article will describe only broad categories. One functional category of proteins is structural.[13] Comparable to cement or concrete used in construction, these proteins give physical cohesion to living organisms at both cellular and macroscopic levels. A second functional category of proteins consists of catalysts for virtually all chemical reactions tak-

13. Examples of structural proteins include tubulin (cytoskeleton), collagen (bones, tendons, skin), and elastin (ligaments, tendons, skin).

ing place in the living cell. Known under the generic name of enzymes, these proteins are ubiquitous and extremely diverse. They play a key role in all chemical reactions necessary to metabolism, as well as in the processes of transcription and translation described above. A third functional category of proteins carry out intercellular communications. Examples of proteins in this category include growth hormone, insulin, ACTH, vasopressine, interleukines, interferons, and G-CSF. While the proteins just described are located in the extracellular space and transmit signals between cells, other proteins involved in intercellular communication are bound to the cellular surface. Known under the generic term of receptors, they transmit signals from outside the cell to the relevant intracellular structure. In addition to binding endogenous hormones and cytokines, receptors are the main target of drugs. The final functional category of proteins helps an organism defend itself against foreign aggressions. Membrane-bound or free in the extracellular space, these proteins, called antibodies, play a major role in immunity.

All proteins can potentially be found in, and purified from, existing organisms. However, the quantities present in organisms are usually very small, resulting in both high purification costs and supply problems. In addition, purification issues, such as unwanted viral contamination, commonly occur.[14]

The advent of recombinant technology has provided a solution to these problems.[15] By inserting the DNA information encoding a desired protein into certain simple or well-studied cells or organisms, the scientist can direct the latter to produce the protein in great quantities, at low cost, and in a form easily amenable to purification. This process has been a focus of biotechnology since its inception.

Before one can insert DNA or a gene into a given cell or organism, it must be in the form of a molecule or its DNA sequence must be known. The traditional way to obtain the sequence is to start from a known protein with a defined biologic function and proceed upstream to the DNA (gene) encoding it. All genes which correspond to proteins currently produced by recombinant means were obtained by this approach.

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14. The unfortunate example of Factor VIII extracted from a blood donor and used to treat hemophilia while contaminated with HIV is still vivid. *See generally* Andrew Rosenthal, *Blood, Money, and AIDS: Hemophiliacs Are Split; Liability Cases Bogged Down in Disputes*, N.Y. TIMES, June 11, 1996, at D1.

15. Another approach, involving the total chemical synthesis of proteins, could eliminate the purification issue but not the cost problem.

Initially, this approach involves purifying and sequencing the protein in order to determine its partial or complete amino acid sequence. Once the latter is known, one can devise and synthesize corresponding partial DNA sequences based on the translation pattern of the genetic code.[16] In order to take into account the degeneracy of the genetic code, multiple DNA sequences — all encoding the partial amino acid sequence in question — must be synthesized. While these short DNA sequences do not contain enough information to encode the complete protein, they may be used as probes to definitively isolate the complete DNA sequence from a DNA library. DNA libraries contain either the total DNA existing in a cell (gDNA)[17] or the DNA transcripted into mRNA along with the encoding for proteins (cDNA).[18] The latter is much smaller than the former as well as easier to work with. The short DNA probes are then labeled with a radioisotope and added to the DNA library. By way of base complementarity in a process called hybridization, the probe corresponding to the correct, full-length DNA in the library will "stick" to and localize the DNA. The DNA is then inserted in a suitable vector for production of the desired protein in a simple, or well-studied, host cell or organism as mentioned above.[19] A vector is generally a circular piece of DNA (plasmid) containing all additional sequences required to express the desired gene in a given cell. A typical bacterial plasmid contains the sequences illustrated below (see Figure 3).

16. For economic and practical reasons, typically only a short DNA sequence (oligonucleotide) is synthesized. The length required for unambiguous matching is determined by the size of the DNA library in which the DNA sequences will be used as probes.

17. gDNA stands for genomic DNA; the genome being the entire DNA component of a cell.

18. cDNA stands for complementary DNA. It refers to the method used to make the library; starting from mRNA and making complementary DNAs by reverse transcription. The distinction between gDNA and cDNA is relevant to superior organisms, for whom genomic DNA is only partially transcribed into RNA due to the presence of introns (non-coding regions of DNA). For lower organisms such as yeast, the distinction is not relevant since most genomic DNA is transcribed into RNA (no introns).

19. The host cell is generally a bacteria, yeast, or other isolated cell. In some cases however, a whole multicellular organism is used for expression of recombinant proteins. This involves specific techniques called transgenic technology.

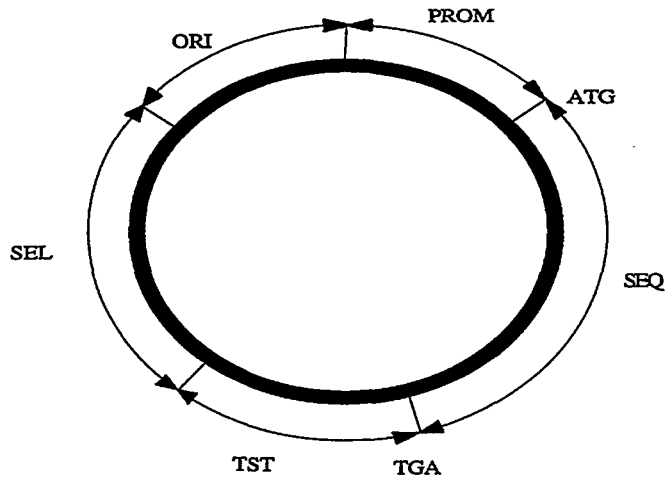

Figure 3. Schematic representation of a plasmid.

ORI : Sequence directing the cell to replicate the plasmid itself (binding-site for DNA polymerase).

PROM : Sequence directing the cell to initiate transcription into RNA (binding-site for RNA polymerase).

ATG : Start codon, indicating the beginning of translation into protein.

SEQ : Inserted protein sequence.

TGA : Stop codon, indicating the end of translation into protein (TAA, TAG is also possible).

TST : Transcription stop, sequence directing the cell to end transcription into RNA (releasing-site for RNA polymerase).

SEL : Marker for the cell (usually antibiotic susceptibility).

The protein sequence excepted, a functional plasmid sequence must be compatible with the expression system (cell or bacteria) in question. Plasmids are sometimes engineered to have compatibility with multiple expression systems or with other customized features. As a result, innumerable different plasmids are conceivable depending on their intended purpose.

The approach to recombinant technology just described proceeds upstream from a known protein to an unknown gene. Recent technology, developed in the context of NIH's Human Genome Project, proceeds inversely: from a known gene to an unknown protein. By systematically sequencing all the human genome, or all cDNA contained in given cDNA libraries, this approach has already re-

vealed the complete DNA sequence of thousands of previously unknown genes. However, knowledge of the DNA sequence alone does not explain the biologic function of the corresponding protein. The only way to determine the biologic function — cloning the thousands of retrieved sequences and examining the properties of the corresponding proteins — is certainly not feasible. Although indirect remedies will be devised, an information gap persists between the sequence of the genes and their function.[20] Nevertheless, once complete, the sequencing of the human genome will greatly simplify the hybridization step required by the traditional protein to gene approach. Indeed, it will replace the actual hybridization of DNA probes by a mere computer search; enabling comparison of the DNA sequences deduced from the known protein with the sequences of the whole genome or sequences contained in selected cDNA libraries.

The techniques mentioned above were developed to produce natural proteins in sufficient quantities in a cost-effective way. As such, natural proteins may make excellent drugs. However, despite their long evolution, natural proteins sometimes have drawbacks from a therapeutic or pharmacological point of view. For example, their pharmacological half-life might be too short or their potency insufficient for the treatment of a specific disease. As a result, protein chemists now try to devise second-generation proteins that are better suited for the intended purpose.

Two distinct approaches can be taken for designing second-generation proteins. First, minor modifications can be made in the sequence of the natural protein obtain a new protein with only one or a few substituted amino acids. This can be done by site-directed mutagenesis, a technique by which one can perform point mutations at the DNA level which are translated to the protein.[21] The other approach to second-generation protein design involves the addition of functional domains originating in other proteins to first-generation

20. This same gap renders the patentability of such "anonymous" DNA sequences questionable on utility grounds. *See* 35 U.S.C. § 101 (1988).

21. Mark J. Zoller & Michael Smith, *Oligonucleotide-directed Mutagenesis Using M13-Derived Vectors: An Efficient and General Procedure for the Production of Point Mutations in any Fragment of DNA,* 10 NUCLEIC ACIDS RES. 6487, 6487 (1982). Methods of site directed mutagenesis include the system of Zoller and Smith using single stranded DNA and of Morinaga using heteroduplexed DNA. *Id.* at 6487. *See also* Yasushi Morinaga et al., *Improvement of Oligonucleotide-Directed Site-Specific Mutagenesis Using Double-Stranded Plasmid DNA,* BIO/TECHNOLOGY, July 1984, at 636. The new protein can also be obtained by total chemical synthesis of the modified protein, albeit at a cost probably incompatible with commercialization. R.B. Merryfield, *Solid-Phase Peptide Synthesis I. The Synthesis of a Tetrapeptide,* 85 J. AM. CHEMICAL SOC'Y 2149 (1963).

proteins. As a result, the new protein bears properties derived from both original proteins. Not yet a practical reality, such an endeavor requires a prior determination of the significance of functional domains, and identification of their amino acid and DNA sequences.[22]

II. OBVIOUSNESS AND THE CHEMICAL ART

To be patentable, an invention is required by the Patent Act to be useful, novel, and nonobvious.[23] These three material conditions apply to a whole range of inventions covered by utility patents. The last of these conditions, nonobviousness, is without contest one of the most difficult concepts in patent law. The historical development of the standard has been conflicting and confusing and remains so today, although to a lesser extent. In addition, the nature of the chemical and biotechnology arts render the application of the standard for nonobviousness especially challenging.

A. Historical Developments and Current Standard

Under the original Patent Act of 1793, utility and novelty were the only material requirements for patentability. In subsequent Patent Acts from 1836 to 1952, a procedural provision indirectly suggested that something more than only novelty and usefulness was required for patentability. In this provision, the Act directed the Commissioner of Patents to issue a patent on an invention if the Commissioner deemed it to be *sufficiently* useful and important.[24] For reasons that are unclear, courts never relied on this provision in their decisions, even when the facts could have supported it.[25]

As early as 1825, defendants in infringement cases began to argue that an invention could not be patented merely because it was new and useful, as stated in the Act. In *Earl v. Sawyer*,[26] the court vehemently denied that anything more than novelty and usefulness was necessary to obtain a patent. The patent involved a shingle sawmill using a circular saw, whereas prior art shingle mills used perpendicular saws. In a clear-sighted statement, Justice Story said, "I am utterly at loss to give any other interpretation of the Act; and,

22. The task is complicated by the fact that functional domains are sometimes composed from non-adjacent regions.

23. 35 U.S.C. §§ 101-103 (1988).

24. Law of July 4, 1836, ch. 357, § 7, 5 Stat. 117, 120 (1836) (current version at 35 U.S.C. § 101 (1988)).

25. *See, e.g.*, Hotchkiss v. Greenwood, 52 U.S. (11 How.) 248 (1850).

26. Earl v. Sawyer, 8 F. Cass. 254 (C.C.D. Mass. 1825) (No. 4,247).

indeed, in the very attempt to make that more clear, . . . there is danger of creating an artificial obscurity . . . ."[27]

However, in *Hotchkiss v. Greenwood*,[28] an 1851 infringement case, the Supreme Court decided otherwise, holding that patentability required something more demanding than only novelty and usefulness.[29] The invention concerned a porcelain doorknob whose inventive shape was disclosed in the prior art. The only difference was that prior art doorknobs were made of metal instead of porcelain:

> unless more ingenuity and skill were required . . . than were possessed by an ordinary mechanic acquainted with the business, there was an absence of that degree of skill and ingenuity which constitute essential elements of every invention. In other words, the improvement is the work of the skillful mechanic, not that of the inventor.[30]

After *Hotchkiss v. Greenwood,* Justice Story's prophecy was realized: the law became obscure. The amorphous test described in the case took various names — inventive novelty, invention, nonobviousness — and was applied in conflicting ways during the following century. During the final period of the evolution that occurred before the Patent Act of 1952, courts, and especially the Supreme Court, gradually became exceedingly severe in applying the standard for nonobviousness. Deviling the monopolistic aspect of patents, the Supreme Court went as far as to require a "flash of inventive genius" from the inventor before granting a patent.[31]

The Patent Act of 1952 was enacted by Congress partly in reaction to these increasingly stringent requirements. Section 103(a) on nonobviousness was intended to codify the principles spelled out in various judicial decisions[32] and was considered as one of the most important aspects of the new Patent Act.[33]

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27. *Id.* at 255. For historical events that occurred before Hotchkiss v. Greenwood, see JOHN W. SCHLICHER, PATENT LAW: LEGAL AND ECONOMIC PRINCIPLES § 5.03 (1995).

28. Hotchkiss v. Greenwood, 52 U.S. (11 How.) 248 (1850).

29. *Id.* at 256. According to Harold C. Wegner, the Supreme Court received inspiration for this doctrine from George Tickemor Curtis' 1849 original treatise on patents. HAROLD C. WEGNER, PATENT LAW IN BIOTECHNOLOGY CHEMICALS & PHARMACEUTICALS 220 (2d. ed. 1994).

30. Hotchkiss v. Greenwood, 52 U.S. (11 How.) 248, 266 (1851).

31. Cuno Engineering Corp. v. Automatic Devices Corp., 314 U.S. 84 (1941) (thermostat-controlled cigarette lighter when both thermostat and lighter were in separate prior art references). *See also* Great Atlantic & Pacific Tea Co. v. Supermarket Equip. Corp., 340 U.S. 147 (1950) (cashier's counter using known mechanical elements).

32. *See, e.g.*, Hotchkiss v. Greenwood, 52 U.S. (11 How.) 248 (1851).

33. S. Rep. No. 1979, 82d Cong. (1952) *reprinted in* 1952 U.S.C.C.A.N. 2394, 2397.

Still valid today, 35 U.S.C. § 103(a) reads as follows:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in § 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner the invention was made.[34]

Unlike previous Patent Acts, § 103(a) clearly states that something more demanding than novelty is required for patentability. The second sentence also provides that the requirement should not go too far, rebuking the "flash of genius" requirement the Supreme Court adopted in *Cuno Engineering Corp. v. Automatic Devices Corp.*,[35] or *Great Atlantic & Pacific Tea Co. v. Supermarket Equipment Corp.*[36] The meaning of § 103 was later clarified in 1966 by the Supreme Court in its landmark case *Graham v. John Deere Co.* which involved an improved chisel plow.[37] The Court held that even though the question of patent validity is one of law, the test of obviousness requires some "basic factual inquiries."[38] The test was spelled out as follows:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or the nonobviousness of the subject matter is determined.[39]

The Court said, "[s]uch secondary consideration as commercial success, long felt but unresolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origins

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34. 35 U.S.C.A. § 103(a) (West. Supp. 1996). As of November 1, 1995, § 103 was divided into three subsections. Section103(a) is identical to the former first paragraph and provides the general test for obviousness, valid for all types of inventions. Section103(b) was enacted in 1995 in reaction to the PTO's excessive interpretation in *In re* Durden (763 F.2d 1406 (Fed. Cir. 1985)) in biotechnology process cases. Pertaining exclusively to processes, § 103(b) is not relevant to our discussion of recombinant products. *Id.* at 1410. Section 103(c) is identical to the former second paragraph of § 103, enacted in 1984. Mostly defining prior art for the purposes of § 103, § 103(c) is not relevant to our discussion.

35. 314 U.S. 84 (1941).

36. 340 U.S. 174 (1950). Section 103 was enacted only two years after *Great Atlantic & Pacific Tea Co. v. Supermarket Equipment Corp.*

37. Graham v. John Deere Co., 383 U.S. 1 (1966).

38. *Id.*

39. *Id.* at 17.

of the subject matter sought to be patented. As indicia of obviousness, these inquiries may have relevancy."[40]

The "may" in the last sentence can now be safely removed. The Federal Circuit has held several times that objective evidence of nonobviousness — the so-called secondary considerations in *Graham* — must always be taken into account and not only in those cases where a doubt remains.[41] The list of admissible objective evidence of nonobviousness has been gradually completed by the Federal Circuit and now includes commercial success, long-felt need, failure of others, unexpected results, evidence of copying, skepticism in the profession, licensing, and laudatory statements by an infringer.[42]

Despite the enactment of § 103 and *Graham,* the law of nonobviousness remained confused. Much debate arose about whether the new Act had changed the law or was only a codification of judicial precedents. The various circuits kept applying conflicting standards, notably for inventions involving a combination of old elements.[43] These inconsistencies certainly contributed to the creation in 1982 of the Court of Appeals for the Federal Circuit.[44]

The clarification of the controversy regarding combination inventions counts among the first accomplishments of the Federal Circuit. For many decades, the Supreme Court had applied a special rule for inventions involving the combination of old elements.[45] The rule was that for a combination invention to be nonobvious the whole had to exceed, in some way, the sum of its parts. Lower courts had trouble consistently applying this "synergistic results" rule for the good reason that virtually all inventions can be considered as the

40. *Id.* at 17-18.

41. *See, e.g.,* Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367 (1986) (sandwich-type immunoassay using monoclonal antibodies). "Objective evidence is not merely icing on the cake." *Id.* at 1380.

42. Robert Merges has legitimately criticized the use of commercial success and other objective evidence of nonobviousness (except for the failure of others) as rewarding marketing and other business-related skills more than significant technical advances. Robert P. Merges, *Commercial Success and Patent Standards: Economic Perspectives on Innovation.,* 76 CAL. L. REV. 803 (1988).

43. *See* 2 DONALD S. CHISUM, PATENTS, § 5.04 [5] (1996).

44. The Court of Appeals for the Federal Circuit was created in good part to achieve uniformity in the application of patent law. Regional doctrinal variation among the various circuits of its predecessor, the Court of Customs and Patent Appeals, had led to legal insecurity and forum shopping. Practically, the Federal Circuit has exclusive appellate jurisdiction in patent cases.

45 *See* Hailes v. Van Wormer, 87 U.S. (20 Wall.) 353 (1874); Great Atlantic & Pacific Tea Co. v. Supermarket Equip. Corp., 340 U.S. 147 (1950); Anderson's Black Rock Inc. v. Pavement Salvage Co., 396 U.S. 57 (1969); Sakraida v. Ag Pro, Inc., 425 U.S. 273 (1976).

combination of old elements. In 1983, the Federal Circuit clearly rejected the rule as being "unnecessary and confusing."[46] As a result, the fact that an invention is a combination of known elements is not relevant to its patentability — only the prior art suggestion or motivation to make the combination is.[47]

In addition, it is useful to mention the notion of "prima facie obviousness" developed by the Federal Circuit principally in chemical and biotechnological cases.[48] It is essentially a procedural tool, used to reverse the burden of proof on the applicant in obviousness cases. The PTO bears the initial burden of proof in establishing a case of prima facie obviousness. It must show "some objective teaching in the prior art or knowledge generally available to one of ordinary skill in the art that would lead that individual to combine the relevant teachings of the references."[49] After the PTO has made this demonstration the applicant can rebut the case of prima facie obviousness with convincing evidence. This generally amounts to a demonstration of some unexpected result or surprising property in the invention.[50]

B. Obviousness of Chemical Compounds

According to Donald Chisum, "claims for chemical compounds present unique problems in applying the standard of non-obviousness or invention. Because of the unpredictable nature of chemical reactions, a newly-synthesized compound may be very similar in structure to known existing compounds and yet exhibit very different properties."[51] It is useful to discuss the reasons underlying both these unique problems and the unpredictability of chemical reactions.

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46 Chore-Time Equip., Inc. v. Cumberland Corp., 713 F.2d 774, 781 (Fed. Cir. 1983). *See also* Environmental Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 698 (Fed. Cir. 1983).

47 *See, e.g.*, Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co., 730 F.2d 1452, 1462 (Fed. Cir. 1984).

48 *In re* Oetiker, 977 F.2d 1443, 1446 (Fed. Cir. 1992). According to the Federal Circuit in *In re* Oetiker, the notion of prima facie obviousness is not limited to chemical practice. Experience shows that it is used mostly in that field. *Id.* at 1446. Although the issue had been implicitly reached in *In re* Papesch and other cases previous to the advent of the Federal Circuit, they do not generally refer to the term "prima facie" obviousness. *In re* Papesch, 315 F.2d 381, 386 (C.C.P.A 1963).

49. *In re* Piasecki, 745 F.2d 1468 (Fed. Cir.1984).

50. For developments on the notion of prima facie obviousness, see ROBERT L. HARMON, PATENTS AND THE FEDERAL CIRCUIT 110-12 (2d. ed. 1991). In chemistry, *see infra* Part II.B.2; KENNETH J. BURCHFIEL, BIOTECHNOLOGY AND THE FEDERAL CIRCUIT 91-95 (1995); and Helmut A. Wegner, *Prima Facie Obviousness of Chemical Compounds,* 6 AMER. PAT. L. ASS'N Q. J. 271 (1978).

51. DONALD S. CHISUM, PATENTS § 5.04[6] (1995) (footnotes omitted).

When it first appeared as a technology, chemistry was unique in that the underlying mechanisms, occurring on a molecular scale, could only be assessed indirectly by techniques revealing the ongoing molecular process. Much of the chemical art that which evolved during the last 250 years amounted to improving this indirect assessment of chemical properties. When they occur in simple systems, such as test tubes, most chemical reactions are now well understood, and fairly predictable. The chemist can accurately foresee what compound(s) will be obtained as a result of a given reaction, what energy level is involved, as well as other specifications. Similarly, the chemist is able to predict some basic properties of the compounds placed in simple systems, such as physicochemical properties, and indirect assessment is sufficiently accurate to avoid a fracture between the structure and the function of the compounds. The unique problems and unpredictable nature of chemical reactions described by Chisum are not results of the mechanics of chemical reactions because these reactions are well understood in simple systems. The determination of obviousness in such cases should be comparable to any mechanical invention.

However, chemical compounds are generally intended for use in highly complex systems, such as living systems. The indirect chemical or biochemical assessment of the reactions taking place in such systems is generally incomplete. Due to the complexity of such systems, a fracture appears between the structure and the properties of the compounds. As a result, the properties of chemical compounds are generally considered as unpredictable.[52] Thus, the strategies and methods for making chemical inventions are different from those used for mechanical inventions. An inventor of a mechanical device can directly envision the structure he needs to solve his problem and can then proceed to invent using known elements with independent mechanical significance.

However, due to the complexity of the systems in which chemical compounds are to be used, the chemist cannot directly envision what structure will confer upon his compound the desired property.

52. Similarly, when the preparation of a product, and not only its effects or properties, involves such a complex system - like biotechnology — the process of obtaining the compound is entached with the same unpredictability. This is the source of a criterion often cited in biotechnology obviousness cases: the reasonable expectation of success (*see supra* Part II.B.1). On the other hand, being an inquiry into living systems, the very activity of biotechnology tends to challenge the presumption of their unpredictability -- notably when thoroughly studied systems are involved (such as *E. coli*, yeast, or others).

Instead, one must start from a known compound.[53] Although the structure-function relationship of chemical compounds is far from being fully understood, its very existence is well established. In comparable systems, structurally similar compounds generally have similar or related properties. Building on this knowledge, the chemist incrementally modifies the prior art compound by adding or subtracting chemical radicals[54] having no independent chemical significance or function. By improving the odds of designing useful compounds, this strategy of "molecular modification" confers some predictability to an otherwise random process. Thus, in the process of molecular modification, the prior art provides the skilled person with suggestions or motivation to make a compound. In this context the determination of obviousness should involve different subtests depending on the subject matter at hand.

In a long line of cases relating to obviousness of chemical compounds, courts have tried to articulate the strategy of molecular modification with the unpredictability of structure-function relationships. The case law is very technical and sometimes conflicting. Some cases deal with prima facie obviousness of chemical compounds whereas others deal with ultimate obviousness.[55] Some cases analyze whether a given structural analogy is sufficient to trigger the presumption of obviousness. Others evaluate the ability of unexpected properties to rebut it. Still other cases establish what beyond structural similarity is needed to trigger a prima facie case. Eventually, all cases attempt to balance the apparent obviousness of structurally similar compounds with the apparent nonobviousness of their unpredictable properties. The Federal Circuit recently summarized the law of chemical obviousness in its much debated[56] en banc rehearing of

53. The chemist can also make random compounds, relying on serendipity, but this approach is inefficient. Serendipity — a term commonly used in medicinal chemistry — means accidental discovery.

54. Chemical radicals are small parts of molecules ubiquitously found in organic molecules. Methyl (-CH_3-) is a typical radical.

55. The nuance between both notions has often been overlooked by authors and courts. Although the material legal issues are similar in both situations, the procedural consequences for the applicant are very different. If the latter can avoid a finding of prima facie obviousness, his invention is patentable without further inquiry. If, inversely, his invention is found prima facie obvious, the applicant must rebut the presumption — most often with costly comparative studies of prior art and new compounds.

56. *See* the vehement dissenting opinion by Judge Newman, joined by Judges Cowen and Mayer. *In re* Dillon, 919 F.2d 688, 699 (Fed. Cir. 1990) (en banc). *See also* Margaret M. Wall & Justin Dituri, *The En Banc Rehearing of In Re Dillon: Policy Consideration and Implications for Patent Prosecution,* 68 DENV. U. L. REV. 261 (1991).

In re Dillon.[57]

Rather than describing the chronological evolution of the case law, which is often illogical, this article will describe the steps currently required for determining the obviousness of chemical compounds. The relevant past case law relating to each step in the respective sections will be mentioned.

The first step is carried out by the Patent and Trademark Office (PTO), or the court, and consists of deciding whether or not the compound is prima facie obvious. This concept is based on the assumption that structurally similar compounds have similar properties and that the disclosure of a compound having some utility in the prior art provides the suggestion to make analogs.

Three conditions must be satisfied for a finding of prima facie obviousness:

(a) Structural similarity between claimed and prior art compounds;
(b) Prior art suggestion or motivation to make the new compound;[58]
(c) A method of making the claimed compound is disclosed in, or rendered obvious by, the prior art (enabling disclosure).

If any one of the above conditions is not satisfied, the compound is deemed nonobvious and patentable without further inquiry.[59] If all three conditions are met, the compound is deemed prima facie obvious. The applicant can then, in a second step, rebut the presumption of obviousness by showing either that the court or the PTO had improperly concluded that all conditions for a prima facie case were met or that the new compound has unexpected properties when compared to the prior art. See Table 1.

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57. *In re* Dillon, 892 F.2d 1554 (Fed. Cir. 1989); 919 F.2d 688 (Fed. Cir. 1990) (en banc).

58. Until 1971, the law was unclear as to whether the second element was required for a finding of prima facie obviousness. Structural similarity alone was seemingly considered as being a sufficient motivation to make the analog. In re *Stemninsky* clearly held that suggestion or motivation was a distinct requirement from structural similarity. In re *Stemninsky*, 444 F.2d 581 (C.C.P.A. 1971).

59. "Because we reverse on the basis of failure to establish a prima facie case of obviousness, we need not reach the issue of the sufficiency of the showing of unexpected results." *In re* Geiger, 815 F.2d 686, 688 (Fed. Cir. 1987) (method of inhibiting corrosion of metallic parts in water cooling systems).

TYPE OF INVENTION	STATUTORY DISPOSITION APPLICABLE	INVENTION IS "OBVIOUS TO A SKILLED PERSON" IF PRIOR ART PROVIDES ("PRIMA FACIE" OBVIOUSNESS)	FACTOR USUALLY REDEEMING PATENTABILITY ("PRIMA FACIE" REBUTTAL)
Chemical compounds (traditional chemistry)	35 U.S.C. § 103(a): "A patent may not be obtained . . . if the . . . subject matter . . . would have been obvious to a person having ordinary skill in the art . . ."	Structurally similar compound(s) + motivation to make the new compound (i.e., some useful property in the prior art compound) + enabling disclosure of a method to make the new compound	Unexpected properties in the new compound or no proper similarity, motivation, or disclosure

Table 1. Obviousness of chemical compounds.

1. Prima Facie Obviousness of Chemical Compounds

a. Sufficient Structural Similarity

It is impossible to determine in the abstract what constitutes sufficient structural closeness of compounds for prima facie obviousness purposes. It depends intimately upon whether the assertion that similar compounds have similar properties is true for the class of compounds at stake. This can be done only on a case by case basis. Most of the early chemical case law dealt with this question of structural obviousness — examining a wide range of classes of organic compounds. The doctrine establishing the relevance of structural similarity to chemical obviousness was first spelled out in *In re Hass*[60] and *In re Henze.*[61] In both cases, prior art and claimed compounds were structurally very close (chemical homologues[62]). Many other cases have shown that other structural similarities can serve as grounds for prima facie obviousness.[63] Nevertheless, as the Federal

60. *In re* Hass, 141 F. 2d 127 (C.C.P.A. 1944) (nitroolefins).

61. *In re* Henze, 181 F. 2d 196 (C.C.P.A. 1950) (anti-convulsant hydantoins).

62. Chemical homologues are serial compounds differing only by a group (-CH_2-).

63. Adjacent and non-adjacent homologues, aliphatic isomers, N-alkyl substituted

Circuit held in *In re Grabiak,* "generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other."[64] Indeed, in *Grabiak* and other cases, the initial PTO finding of prima facie obviousness was reversed precisely because the claimed compounds lacked sufficient structural similarity with the compounds in the prior art.[65] In such cases, the prior art and the structure of claimed compounds were found to be too different to verify the assertion of similar properties. Although rebutting a prima facie obviousness determination most often involves a showing of unexpected properties in the new compounds,[66] such cases demonstrate that the same may be accomplished by showing that the prior art and claimed compounds are in fact not sufficiently similar.

b. Prior Art Suggestion or Motivation to Make the New Compound

In early cases, structural similarity appeared sufficient to constitute prima facie obviousness.[67] In other words, the very disclosure of a chemical compound was considered a sufficient motivation to make analogs — independent of any other concern. However, this reasoning was questionable since it could be applied to molecular modifications performed on any of the innumerable chemical compounds disclosed in the art. In *Stemninsky* the Court of Customs and Patent Appeals (CCPA) found that prior art disclosure of a structural analog alone was insufficient to provide real motivation to make a new compound.[68] The applicant claimed a tin composition useful in lubricants as an antioxidant — the prior art analog compositions had no known utility. The court decided that without a known utility for

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amines, alkylated aromatic compounds, aromatic position, aliphatic position isomers, ethers, esters of prior art alcohols, reverse esters, halogen analogs, and chalkogens have sometimes been considered by the PTO, or the courts, as sufficiently similar in structure to trigger a prima facie obviousness case. For details about this very technical aspect of chemical patent law, see Helmut A. Wegner, *Prima Facie Obviousness of Chemical Compounds*, 6 AM. PAT. L. ASS'N Q.J. 271 (1978) and HAROLD C. WEGNER, PATENT LAW IN BIOTECHNOLOGY, CHEMICALS & PHARMACEUTICALS 278 (2d. ed. 1994) (both references cite relevant cases).

64. *In re* Grabiak, 769 F.2d 729, 731 (Fed. Cir. 1985) (claimed thioester and prior art ester useful as herbicidal safeners).

65. *See, e.g., In re* Jones, 958 F.2d 347 (Fed. Cir. 1992); *In re* Hedges, 783 F.2d 1038 (Fed. Cir. 1986); *In re* Grabiak, 769 F.2d 729 (Fed. Cir. 1985); *In re* Grose, 592 F.2d 1161 (C.C.P.A. 1979); *In re* Taborsky, 502 F.2d 775 (C.C.P.A. 1974); *In re* Elpern, 362 F.2d 762 (C.C.P.A. 1964); *In re* Mills, 281 F.2d 218 (C.C.P.A. 1960).

66. *See infra* Part II.B.2.

67. *See, e.g., In re* Riden, 318 F.2d 761 (C.C.P.A. 1963); *In re* Henze, 181 F.2d 196 (C.C.P.A. 1950).

68. *In re* Stemninsky, 444 F.2d 581 (C.C.P.A. 1971).

the prior art compounds, the applicant had no reason or motivation to synthesize the claimed analogs. It was also immaterial that the prior art compounds actually had these properties since they were unknown at the time of invention. Accordingly, the new compounds in *Stemninsky* were deemed nonobvious and patentable. A subsequent line of cases confirmed *Stemninsky*.[69] The conclusion of these cases is that some utility for the prior art compound is required in order to give the skilled person a general motivation to make analogs.[70] Only then can the new compound be deemed prima facie obvious. The court in *In re Gyurik* properly summarized the situation:

> An element in determining obviousness of a new chemical compound is the motivation of one having ordinary skill in the art to make it. That motivation is not abstract, but practical, and is always related to the properties or uses one skilled in the art would expect the compound to have, if made.[71]

Finally, the Federal Circuit refined the theory in its en banc rehearing of *In re Dillon*.[72] The applicant claimed a composition of hydrocarbon fuel and tetra-orthoester producing less soot during combustion; the prior art disclosed the use of tri-orthoesters in fuel for dewatering purposes and of tetra-orthoesters as water scavengers in hydraulic fluids. The court found that the properties disclosed in the prior art analogs (dewatering and water scavenging) were sufficient to motivate the applicant to make her analogous composition, even though the claimed property (reduced soot emission) was not suggested in the references. In other words, the Federal Circuit decided that the inquiry regarding the properties of prior art compounds, done for the purposes of establishing motivation,[73] was distinct and independent from the inquiry concerning unexpected

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69. *See, e.g., In re* Gyurik, 596 F.2d 1012 (C.C.P.A. 1979) (holding the anthelminthic process of a structural analog not obvious from use as an intermediate in a reaction). *See also In re* Lalu, 747 F.2d 703 (Fed. Cir. 1984) (finding the use of sulfonyl chlorides in corrosion inhibiting agents not obvious from prior use as intermediates in the production of sulfonic acid). *Cf. In re* Albrecht, 514 F.2d 1385 (C.C.P.A. 1975) (involving a prior art compound having useful properties but also undesirable side-effects). Note that in *In Re* Albrecht, the ruling is questionable because one could have been motivated by the prior art compound to prepare an analog retaining the useful properties, but lacking the undesirable side-effects.

70. Although the existing case law discusses only the utility or properties of prior art compounds as motivation to make the new compounds, one can imagine other "motivating" facts.

71. *In re* Gyurik, 596 F.2d 1012, 1018 (C.C.P.A. 1979).

72. *In re* Dillon, 919 F.2d 688 (Fed. Cir. 1990) (en banc), *reh'g of In re* Dillon, 892 F.2d 1554 (Fed. Cir. 1989).

73. *See supra* Part II.B.1.b.

properties of the claimed compound made to rebut a finding of prima facie obviousness.[74] The previously disclosed properties of a prior art compound can provide sufficient motivation to trigger a prima facie obviousness objection, even though the new compound has unrelated, different, and unexpected properties. It is then the applicant's responsibility to rebut the presumption by showing that his compound has unexpected properties relative to prior art compounds.[75]

The *Dillon* court said:

> [S]tructural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness .... [T]he burden (and opportunity) then falls on an applicant to rebut that *prima facie* case .... [I]t is not necessary in order to establish a *prima facie* case of obviousness that both a structural similarity between a claimed and prior art compound (or a key component of a composition) be shown and that there be a suggestion in or expectation from the *prior art* that the claimed compound or composition will have the same or a similar utility as *one newly discovered by applicant.*
>
> ....
>
> Properties ... *are* relevant to the creation of a *prima facie* case in the sense of affecting the motivation of a researcher to make compounds closely related to or suggested by a prior art compound, but it is not required, as stated in the dissent, that the prior art disclose or suggest the properties newly-discovered by an applicant in order for there to be a *prima facie* case of obviousness.[76]

When the claimed compound is included in a large genus previously disclosed in the prior art, questions might arise as to its patentability. Previously treated mostly as an anticipation matter,[77] this issue is now more often raised during obviousness analysis. The Federal Circuit now considers that such compounds are not only

74. *See infra* Part II.B.2.

75. *See infra* Part II.B.2.

76. *In re* Dillon, 919 F.2d at 692-97.

77. Disclosure of a chemical genus is generally not an adequate disclosure of the individual compounds for the purposes of anticipation. *In re* Arkley, 455 F.2d 586 (C.C.P.A. 1972); *In re* Ruschig, 343 F.2d 965 (C.C.P.A. 1965). Anticipation requires either that the compound be individually disclosed in the prior art or that it be disclosed as a member of a "small recognizable class [of compounds] with common properties." *In re* Ruschig, 343 F.2d 965, 974 (C.C.P.A. 1965) (requiring that a compound be individually disclosed in prior art, or part of a small recognizable class of compounds).

novel but also nonobvious unless something in the prior art motivates the skilled person to select the claimed compound among the multitude included in the genus.[78] This motivation goes somewhat beyond the mere prior art disclosure of a structural analog and its properties as required in the *Heinz-Henze* and *Stemninsky-Dillon* lines of cases.

Similar to what has been said above about insufficient structural similarity, even though the rebuttal of a prima facie obviousness determination usually involves a showing of unexpected properties,[79] it can also be done by showing that the prior art is so deficient that it does not provide a motivation to make the new compound.

For the purposes of this discussion, the notion of suggestion or motivation is used in the narrow sense of "suggestion or motivation to make a specific molecular modification" or "chemical suggestion" because this is the terminology found in the *In re Stemninsky* line of cases. The broader "suggestion test" for obviousness as understood in the mechanical art would include both structural analogy and suggestion in the narrow sense (prior art property). In other words, for the prior art to provide complete suggestion or motivation leading to prima facie obviousness the motivation originating from a prior art analog chemical structure acting as template (*Hass-Henze*) must be supplemented by the knowledge that the latter has some utility or property (*Stemninsky-Dillon*).

c. Enabling Disclosure and Reasonable Expectation of Success

Before a prima facie case of obviousness can be made, the prior art must also show how to practice the invention — disclose or render obvious a process indicating how to make or obtain the claimed compound — in addition to sufficiently similar compounds and suggestion or motivation (narrow sense). The issue is often not even mentioned in traditional chemical cases because most molecular modifications are easily performed according to standard organic chemistry reactions. Nevertheless, in a few relevant cases the prior art did not disclose or render obvious a method able to make the otherwise obvious compound. The courts decided that the lack of an

78. *See, e.g., In re* Baird 16 F.3d 380 (Fed. Cir. 1994); *In re* Jones, 958 F.2d 347, (Fed. Cir. 1992). Note also the similarity to *In re* O'Farrell, holding that improper "obvious to try" rejections include inventions where one must "vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *In re* O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988).

79. *See infra* Part II.B.2.

enabling disclosure in the prior art rendered the compounds themselves nonobvious and patentable.[80]

In *In re Hoeksema*,[81] the applicant claimed a furanoside similar to others disclosed in the prior art. He argued that since no prior art process was able to yield his compound the latter was patentable notwithstanding structural similarities or unexpected properties:

> Despite this close structural similarity between the De Boer amino compound [prior art] and the alkylamino and dialkylamino compounds included in the appealed claim, appellant chose not to submit a showing of unexpected properties in his claimed compounds. Appellant asserted that his compounds were unobvious and patentable without such a showing. He urged that De Boer does not teach one of ordinary skill in the art how to make appellant's claimed compounds, and the examiner did not cite any other reference telling how they might be made.[82]

The court agreed with the appellant:

> In the context of section 103, we are not permitted to fragment a claimed invention in applying that section. The clear mandate of the statute which governs our analysis requires that we consider the invention as a whole in making the determination.
>
> Thus, as we apply the statute to the present invention, we must ask first, what is the invention as a whole? Necessarily, by elementary patent law principles, it is the claimed compound, but, so considered, unless there is some known or obvious way to make the compound, the invention is nothing more than a mental concept expressed in chemical terms and formulae on a paper.
>
> *We are certain, however, that the invention as a whole is the claimed compound* and *a way to produce it*, wherefore appellant's argument has substance.[83]

The court properly summarized the issue as follows:

> If the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that

80. *See In re* Hoeksema, 399 F.2d 269 (C.C.P.A. 1968); *In re* Brown, 329 F.2d 1006 (C.C.P.A. 1964); *see also In re* Dow Chemical Co., 837 F.2d 469 (Fed. Cir. 1985); *Cf. In re* Payne, 606 F.2d 303 (C.C.P.A. 1979) (enabling disclosure found).

81. *In re* Hoeksema, 399 F.2d 269 (C.C.P.A. 1968).

82. *Id.* at 271 (footnote omitted).

83. *Id.* at 273 (emphasis added).

> the compound itself is in the possession of the public. In this context, we say that the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious, based on close relationships between their structures and those of prior art compounds.[84]

Thus, in addition to the arguments discussed here,[85] prima facie obviousness can be rebutted by showing that the prior art does not provide an enabling disclosure, i.e., a method which enables one to practice the invention with a reasonable expectation of success. This explains why the inquiry into obviousness of products proposed as patentable inventions must sometimes focus on the method used to make or obtain them.[86]

As noted above, the importance of an enabling disclosure in the context of product obviousness is diminished in the field of traditional chemistry, where a compound first formulated on paper is generally easy to make by following standard synthesis methods. However, it becomes most important in biotechnology products which are often obtained after complicated and initially unreliable processes. As a result, in many biotechnology cases, the "reasonable expectation of success" of the method used to obtain the product has become the measure of obviousness for the product itself. Such products are usually widely suggested in the prior art and made precisely to have specific, expected properties. Accordingly, biotechnology products are ill-suited for the rebuttal arguments of lack of suggestion or unexpected properties which are usually invoked against prima facie obviousness in traditional chemical cases. In addition, first generation biotechnology products are generally naturally-occurring products. In such cases, the contribution of the inventor typically resides in the discovery itself rather than in the design of a new structure — either by molecular modification or *de novo*. In situations where the prior art provides a general method for systematically making discoveries, like in biotechnology, some inquiry into the discovery process is appropriate when examining obviousness issues.

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84. *Id.* at 274 (footnote omitted). Further case law discusses how reliable the method should be to constitute an enabling disclosure. According to the law of enablement (35 U.S.C. § 112), an "enabling" method should not require undue experimentation from the skilled person to practice the invention. In other words, it must provide a reasonable expectation of success to obtain the invention. *In re* Dow Chem. Co., 837 F.2d 469 (Fed. Cir. 1985).

85. *See* discussion *supra* Parts II.B.1.a, II.B.1.b; *see also* discussion *infra* Part II.B.2.

86. The Federal Circuit has difficulty accepting this notion. *See In re* Deuel, 51 F.3d 1552, 1559 (Fed. Cir. 1995); *In re* Bell, 991 F.2d 781, 785 (Fed. Cir. 1993).

For all these reasons, "reasonable expectation of success" issues arise mostly in biotechnology cases and have until recently provided the main rebuttal argument against prima facie obviousness findings in biotechnology products.[87]

2. Rebuttal of the Presumption (Unexpected Properties)

An applicant may rebut the presumption of obviousness in several ways. As noted above, the applicant may show that the new compound is not close enough structurally to known compounds,[88] that the prior art does not provide suggestion or motivation to make it,[89] or a reliable method to obtain it.[90] In addition, the applicant may rebut the presumption of obviousness by proving that the compound has unexpected properties.

This rule was initially set out in *In re Papesch,* where the applicant had claimed a pyrazole compound, whose lower homologue was disclosed in a prior art reference.[91] Faced with a PTO Board rejection for structural obviousness, he unsuccessfully argued that his compound had anti-inflammatory properties not present in the prior art analog compounds. On appeal, the CCPA accepted the argument and overturned the PTO decision holding that "[f]rom the standpoint of patent law, a compound and all of its properties are inseparable."[92] The court affirmed that beyond a compound's structure, contemplation of its properties is required for an ultimate obviousness determination. Accordingly, the court deemed the anti-inflammatory compounds nonobvious and patentable. In this case, the applicant had rebutted a presumption of obviousness based on structural similarity by showing that his claimed compounds had unexpected properties (anti-inflammatory properties) not present in prior art analogs. Although the court in *Papesch* did not use the terminology, the applicant had essentially rebutted a prima facie case of obviousness.

In *Papesch,* the unexpected anti-inflammatory property was present only in the claimed compounds and not in the prior art structural analogs. However, more often than not, newly created compounds differ from prior art either by exhibiting the same property but to a

87. *See, e.g.*, Amgen Inc., v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 1208 (Fed. Cir. 1991); *In re* Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991); *In re* O'Farrell, 853 F.2d 894, 904 (Fed. Cir. 1988); *Ex parte* Erlich, 3 U.S.P.Q.2d (BNA) 1011 (1986).

88. *See* discussion *supra* Part II.B.1.a.

89. *See* discussion *supra* Part II.B.1.b.

90. *See* discussion *supra* Part II.B.1.c.

91. *In re* Papesch, 315 F.2d 381, 382 (C.C.P.A. 1963).

92. *Id.* at 391.

different degree or by exhibiting a new property alongside other common properties. Except in short dicta, none of these issues are directly addressed in *Papesch.*

a. Difference in Degree of a Same Property

After *Papesch,* the courts had to determine whether a difference in degree of a same property would amount to an "unexpected property" sufficient to rebut a prima facie case of obviousness. In dictum, the *Papesch* court hinted at a negative answer by noting "*[a] mere difference in degree* is not the marked superiority which ordinarily will remove the unpatentability of adjacent homologues of old substances."[93]

However, the case law gradually began to consider a significant difference in degree of a same property as equivalent to an unexpected property. In *In re Lohr,*[94] the court said that to be so "clear and convincing evidence of substantially greater effectiveness is needed." This principle was reaffirmed in numerous cases and more recently in *In re Chupp,*[95] which involved a herbicide which was demonstrated to be superior to prior art herbicides in combating weeds in some — but not all — crops. The court decided that a superior herbicidal activity constituted an unexpected property for the purpose of rebutting a case of prima facie obviousness:[96] The court noted that "evidence of unobvious or unexpected advantageous properties . . . may include data showing that a compound is unexpectedly superior in a property it shares with prior art compounds.".[97]

Whereas the principle of accepting a difference in degree of a same property as rebuttal of prima facie obviousness is now well settled, much less is known regarding what quantitative superiority in properties is required to be considered unexpected. In *In re Merck,*[98] the applicant claimed a method of treating depression in humans by amitriptyline, a compound having stronger sedative and anticholinergic effects than prior art analogs. Rejecting the claims, the court implied that a quantitative assessment of the differences between prior art compounds and those used in the claimed method would be rele-

93. *Id.* at 392.

94. 317 F.2d 388, 392 (C.C.P.A. 1963) (insecticidal thiophosphate).

95. 816 F.2d 643, 646 (Fed. Cir. 1987).

96. *Id.* at 647. *See also In re* Lunsford, 357 F.2d 380, 385 (C.C.P.A. 1966); *In re* Wagner, 371 F.2d 877, 885 (C.C.P.A. 1967).

97. *In re* Chupp, 816 F.2d 643, 646 (Fed. Cir. 1987) (citation omitted).

98. *In re* Merck, 800 F.2d 1091, 1092 (Fed. Cir. 1986).

vant to the nonobviousness determination: "In the absence of evidence to show that the properties of the compounds differed *in such an appreciable degree* that the difference was really unexpected, we do not think that the Board erred in its determination that appellant's evidence was insufficient to rebut the prima facie case."[99]

In *United States v. Ciba-Geigy,*[100] the court admitted that a thiazide anti-hypertensive compound ten times more potent than those in the prior art was nonobvious and patentable. In *In re Lunsford,*[101] an increase in anti-convulsant potency of 4.4 to 7.0 times was deemed sufficient to patent the claimed compound. Conversely, in *Ex parte Thim,*[102] a proinsulin analog leading to an expression yield 1.6 to 2.0 times greater than prior art proinsulins was found obvious because the yield increase was "not so significantly superior that it overcomes the *prima facie* case of obviousness."[103]

b. Common Properties in Addition to a New Property

In another dictum, the *Papesch* court implied that common properties shared by prior art and claimed compounds would not preclude patentability conferred by a new, unexpected property:

> The argument has been made that patentability is here being asserted only on the basis of *one* property, the anti-inflammatory activity, and that the compounds claimed and the compound of the prior art presumably have many properties in common. *Presumably* they do, but presumption is all we have here.[104]

However, according to subsequent cases in which the issue was directly raised, the existence of significant common properties in addition to new and unexpected ones seems to be viewed as relevant to patentability.[105] In *In re De Montmollin,*[106] the applicant had claimed a dyestuff effective on both cotton and wool, whereas the prior art structural analog was effective on wool only.[107] The court decided

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99. *Id.* at 1099 (emphasis added).

100. United States v. Ciba-Geigy, Corp., 508 F. Supp. 1157, 1172 (D.N.J. 1979) (hydrochlorothiazide).

101. *In re* Lunsford, 357 F.2d 380, 385 (C.C.P.A. 1966).

102. 22 U.S.P.Q.2d (BNA) 941 (Bd. Pat. App. & Int. 1991).

103. *Id.* at 1944. *See also* discussion *infra* Part III.B.

104. *In re* Papesch, 315 F.2d 381, 391 (C.C.P.A. 1963).

105. *In re* De Montmollin, 344 F.2d 976, 978-89 (C.C.P.A. 1965); *In re* Mod, 408 F.2d 1055, 1057 (C.C.P.A. 1969); *In re* Albrecht, 514 F.2d 1385, 1389 (C.C.P.A. 1975); *In re* May, 574 F.2d 1082, 1092 (C.C.P.A. 1978).

106. 344 F.2d 976 (C.C.P.A. 1965).

107. *Id.* at 977.

that structural similarity plus significant common properties rendered the claimed compound obvious. The court noted, "we do not regard the additional ability to dye cotton sufficient to render the subject matter as a whole unobvious. We think the reference teachings provide more than adequate reason to those of ordinary skill for making the present compounds."[108]

The last sentence shows how the court seems to confuse two distinct steps in which properties of prior art compounds are relevant to obviousness. On the one hand, properties are relevant for establishing the motivation necessary for a finding of prima facie obviousness.[109] On the other hand, according to the present line of cases, properties are relevant to an ultimate obviousness determination when common and new properties are compared. Although both issues should be distinguished, the confusion is present in most cases prior to *In re Dillon.*

In another similar case, *In re May,*[110] the court suggested that common and new properties be "balanced" against each others:

> We are of the opinion that a novel chemical compound can be *nonobvious* to one having ordinary skill in the art notwithstanding that it may possess a known property in common with a known structurally similar compound. Thus, merely because those skilled in the art would have expected the compound of claim 11 to have analgesic activity, does not mean, as the board apparently suggests, that an irrebuttable presumption of obviousness has been established. Those properties which would have been expected must be balanced against the unexpected properties.[111]

"Balancing" common and new properties, as suggested by this line of cases, is neither easy nor objective. The rule probably arises from the concern that owners of patented prior art analog compounds would be hurt if a new analog compound sharing significant common properties with their products, with only marginal additional properties, were allowed to enter the market without risking any infringement liability.[112] The "balancing" doctrine will certainly have to be

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108. *Id.* at 979.

109. *See* discussion *supra* Part II.B.1.b.

110. 574 F.2d 1082 (C.C.P.A. 1978).

111. *Id.* at 1093-94 (C.C.P.A. 1978) (quoting *In re* Albrecht, 514 F.2d 1389, 1395-6 (C.C.P.A. 1975)).

112. The only recourse for the patent owner would be either a suit for literal infringement since his compound was probably used as a starting material for making the new one (facing a defense of experimental exemption) or an uncertain suit for infringement under the doctrine of equivalents.

revived in biotechnology, with the advent of second-generation proteins bearing both common and new properties when compared with first-generation proteins.

III. RECOMBINANT INVENTIONS TYPOLOGY

The case law and the criteria for the obviousness determination just described were all developed with traditional chemistry and its principal path to new compounds — molecular modification — in mind. Accordingly, structural similarity with prior art compounds plays a central role in determining obviousness, nuanced by "redeeming" circumstances such as lack of a prior art property *(Stemninsky-Dillon)*, lack of an enabling method *(Hoeksema)*, and unexpected properties *(Papesch)*. However, the range of recombinant inventions amenable to patenting is very diverse, both as to their conception and their differences from the prior art. Accordingly, the obviousness inquiry of § 103 will focus on different subtests, depending on the nature of the subject matter. Although all DNAs and proteins can be considered "chemical compounds,"[113] the subtests which are used in traditional chemistry as described above are not applicable in all cases. Notably, the significance of structural similarity between prior art and claimed compounds, so important in traditional chemistry, makes little sense in relation to recombinant products obtained by means other than molecular modification of prior art compounds. In such cases, a court should return to the original meaning of § 103 on nonobviousness, rather than use rigid subtests which were devised in a different context.

Along these lines, this article will distinguish three categories of recombinant products:

1. "translation" inventions, such as naturally-occurring DNAs. A typical example is the retrieval of the gene encoding for erythropoietin (EPO), based on a method starting from the partial amino acid sequence of the protein. The contribution of the inventor resides in her use of a technique to transform basic information (amino acid sequence plus DNA library or database) from the prior art into another form (DNA sequence). Because this approach allows one to systematically make useful discoveries for the first time in history, none of

113. To a certain extent, every tangible matter could be considered a "chemical compound." The fact that originally only small molecules (and now macromolecules as well) could be defined by their exact chemical formula should not radically change the patent law analysis because it only reflects how subject matter is characterized, rather than the subject matter itself.

the obviousness analysis developed in the chemical or mechanical arts applies. Under current law, and despite the efforts of the Federal Circuit, "translation" inventions are at great risk of being found obvious, as soon as the underlying technology is mature.

2. "molecular modification" inventions, such as second-generation proteins or DNAs obtained by incremental modifications of their sequence. A typical example would be a natural peptidic hormone, modified to have a longer half-life or stronger potency. The inventive step resides in the creation *de novo* of at least some part of the sequence, starting from a prior art sequence as template and substituting, adding, or subtracting elements (amino acids or nucleotides) having no autonomous functional meaning. Due to similarities in the mode of conception, the obviousness analysis developed in the traditional chemical case law applies without major obstacles to such recombinant "molecular modification" inventions.

3. "combination" inventions, such as DNA vectors or second-generation proteins designed by combining prior art functional domains. Typical examples include vectors having promoters compatible with two or more different expression systems or a hybrid protein featuring a functional domain having a specific pharmacological activity and another functional domain allowing a better penetration into the target cell. In such inventions, the contribution of the inventor resides in the very combination of prior art functional units (sequences). Due to similarities in the mode of conception, the obviousness analysis developed in mechanical inventions which combine prior art functional elements also applies without major problems to recombinant "combination" inventions.

This article will now discuss the three categories while integrating the relevant case law.

A. *"Translation" Inventions: Naturally-Occurring DNAs*

The first category of recombinant inventions concerns naturally occurring DNAs, retrieved by starting from the corresponding protein sequence.[114] In such inventions, the contribution of the inventor resides in the discovery of a naturally-occurring structure[115] rather than

114. Or from a partial amino acid sequence long enough to allow the unambiguous localization of the DNA in the library. The minimal size for DNA probes is typically 15 to 25 residues (15 to 25-mers oligonucleotides), depending on the size of the library screened.

115. Strictly speaking, not all DNAs encoding for natural proteins do "occur in nature," due to the presence of introns in the genome of eukaryotic organisms. However, most occur in nature in the form of mRNAs, easily converted in cDNA.

in the creation of a new structure or of part of it. Instead of making incremental modifications to prior art molecules, as in traditional chemistry, the developer of a "translation" DNA starts from the molecular information contained in a prior art protein in order to retrieve the corresponding DNA from a suitable DNA library. Since both the starting material (the prior art protein) and the resulting product (the retrieved DNA) have a similar informational content, encoded in different molecules (or alphabet), these DNAs will be called "translation" inventions.[116] Due to the different mode of conception of "translation" inventions, the case law on chemical and mechanical inventions provides little guidance in deciding obviousness. Since they do not exist in usable form in nature, retrieved "translation" DNAs are patentable subject matter under § 101. Since they were previously undiscovered, they will also generally be new, as required by § 102. However, questions arise as to their obviousness under § 103, because, in order to retrieve the DNA, prior art protein information is used to screen a prior art DNA library or database[117] according to a prior art method.[118] It does not make sense to apply the obviousness analysis relative to the criteria of structural similarity to "translation" DNAs.

In traditional chemistry, the presence of a prior art structural analog is relevant to obviousness because, along with a known property, it provides suggestion and motivation to the skilled person to make a new compound by modifying the prior art analog. The rationale underlying this analysis is that similar compounds generally have similar properties. Since the molecular modification approach has long been the only one (aside from mere serendipity) able to yield new and useful compounds, courts and practitioners have learned to look systematically for structural analogs when determin-

116. Due to the degeneracy of the genetic code, a protein actually contains slightly less information than its corresponding natural DNA and is by itself not sufficient to retrieve it. The resulting information gap is filled by the information contained in the DNA library. Transposed in the linguistic translation metaphor, the degeneracy of the genetic code is equal to the translation of the same notion expressed by a single word in the starting language, and by several alternate words in the receiving language. The basis of the DNA library is a universal language.

117. As already noted, the painstaking process of hybridizing probes in actual DNA libraries will soon be replaced by a computer search.

118. To continue with the linguistic metaphor, whereas a mere translation would reach the level of innovation required for a copyright (originality), it would not reach a level equivalent to nonobviousness in patent law (e.g., to win an originality prize). The level of innovation required by originality in copyright law is generally less demanding than that required by nonobviousness in patent law.

ing chemical obviousness. With time, people forgot the original meaning of the reasoning and started to equate the presence of prior art structural analogs with prima facie obviousness. However, structural similarity is relevant to obviousness almost exclusively in the context of a molecular modification approach involving incremental modification of prior art structures. Section 103 does not require that the prior art disclose a structural analog in all cases. Rather, it requires that the prior art as a whole provide the skilled person with a motivation or suggestion to make the new invention. It follows that suggestion or motivation can be provided by means other than structural analogs, especially when methods other than molecular modification are used. In other words, structural analogs are not required for a finding of prima facie obviousness, even though they constitute a reliable sign when the molecular modification approach is used.[119]

However, in the context of "translation" DNAs, the suggestion or motivation to make the invention is immediately and automatically provided by the general knowledge that producing a protein by inserting the corresponding DNA into a recombinant organism is advantageous. The suggestion arises as soon as a new natural protein is isolated and characterized. As a result, the "suggestion test" (broader sense) is automatically met in virtually all cases of translation DNAs.

We saw previously that when the prior art provides the motivation or suggestion for making an invention, the invention may be nonobvious — hence patentable — if no enabling method is available at the time the invention is made.[120] The measure of an enabling method is that it must allow the inventor to make his product with a reasonable expectation of success.[121] In the context of translation DNAs, the enabling method consists of building degenerate DNA probes from the prior art amino acid sequence and hybridizing them in a suitable DNA library to retrieve the desired full-length DNA.[122]

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119. In the case of translation DNAs, the role played by structural similarity in traditional chemistry is played by the informational similarity between the prior art protein and the DNA. From structural obviousness, we shift to informational obviousness.

120. *See* discussion *supra* Part II.B.1.c. *In re* Hoeksema, 399 F.2d 269 (C.C.P.A. 1968); *In re* Payne, 606 F.2d 303 (C.C.P.A. 1979); *In re* Dow Chem. Co., 837 F.2d 469 (Fed. Cir. 1988).

121. *See In re* Dow Chem. Co., 837 F.2d 469, 472 (Fed. Cir. 1988); *See also In re* O'Farrell, 853 F.2d 894, 904 (Fed. Cir. 1988).

122. This assumes that the prior art protein has already been isolated and purified to an extent allowing at least partial sequencing. I do not include the isolation/purification/sequencing of the protein in the "translation" method. This step sometimes constitutes the nonobvious step on the road to the corresponding DNA. *See, e.g., Ex parte* Maizel, 27 U.S.P.Q.2d (Bd. Pat. App. & Int. BNA) 1662 (1992) (prior art protein mostly char-

Among the criteria used in traditional chemistry cases, the criteria regarding the enabling method makes the most sense in the context of translation inventions. Obviously, the answer to the question of whether the translation method has a reasonable expectation of success will strongly depend on the development stage of the technology.

Finally, the notion of unexpected properties used in traditional chemistry to rebut prima facie obviousness[123] does not add to the analysis in the context of translation DNAs. The properties of DNA, both direct (encoding the desired protein) and indirect (that of the encoded protein),[124] are known in advance and hence expected.

Accordingly, with one exception,[125] case law concerning the obviousness of translation DNAs focuses on whether the method used to obtain the DNA has a reasonable expectation of success.[126] If there is no reasonable expectation of success, the DNA is nonobvious, and patentable.[127] If there is a reasonable expectation of success, the DNA is obvious and unpatentable. The situation is summarized in Table 2.

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acterized by its function did not preclude the patentability of the corresponding DNA because it had not been isolated to sufficient purity allowing sequencing. The application was rejected on other grounds).

123. *See* discussion *supra* Part II.B.2.

124. For the purpose of evaluating unexpected properties of DNAs, both their direct properties and those of the corresponding protein are relevant. *See Ex parte* Anderson, 30 U.S.P.Q.2d (BNA) 1866, 1869 (Bd. Pat. App. & Int. 1993) ("In the case before us, appellants are claiming a DNA and the use of that DNA. What is of concern in the consideration of rebuttal evidence are the properties of the DNA itself and/or the product it produces, i.e., the protein it codes for.").

125. *In re* Deuel, 51 F.3d 1552 (Fed. Cir. 1995).

126. See cases cited in Part III.A.1.

127. This implies that the applicant has brought some nonobvious improvement to the prior art method to render it "enabling."

TYPE OF INVENTION	STATUTORY DISPOSITION APPLICABLE	INVENTION IS "OBVIOUS TO A SKILLED PERSON" IF PRIOR ART PROVIDES	FACTOR USUALLY REDEEMING PATENTABILITY
Translation inventions (DNAs obtained from the corresponding protein)	35 U.S.C. § 103(a): "A patent may not be obtained . . . if the . . . subject matter . . . would have been obvious to a person having ordinary skill in the art . . ."	"basic information" underlying invention (protein sequence) + method of "translation"	no reasonable expectation of success of the method of "translation"

Table 2. Obviousness of "translation" inventions.[128]

This article will next describe the approach to "translation" inventions before and after *In re Deuel*,[129] which represents a clear departure from the logic of earlier cases.

1. Before *In re Deuel*

The decisions by the Federal Circuit and the PTO Board of Patent Appeals and Interferences appear to be split in their ultimate assessment of the obviousness of translation inventions. Two Federal Circuit cases, *Amgen v. Chugai*,[130] and *In re Bell*,[131] where the inventions were found patentable, held the prior art "translation" method as arcane and not enabling (not apt to yield the claimed DNAs with a reasonable expectation of success). The decisions singled out nonobvious improvements of the method by the applicant and or his departure from prior art teachings. Other decisions by both the Federal Circuit and the PTO Board acknowledge the increasingly routine character of the translation process, and deem obvious the claimed DNAs.[132] Importantly, whatever the ultimate decision on obvious-

128. Although the Federal Circuit considers that the notion of "prima facie" obviousness applies to any invention (*In re* Oetiker, 977 F.2d 1443 (Fed. Cir. 1992)), the issue is mentioned almost exclusively with molecular modification inventions.

129. *In re* Deuel, 51 F.3d 1552 (Fed. Cir. 1995).

130. 927 F.2d 1200 (Fed. Cir. 1991).

131. 991 F.2d 781 (Fed. Cir. 1993).

132. *Ex parte* Hudson, 18 U.S.P.Q.2d (BNA) 1322, 1325 (Bd. Pat. App. & Int. 1990); *Ex parte* Deuel, 33 U.S.P.Q.2d (BNA) 1445, 1449 (Bd. Pat. App. & Int. 1993); *Ex parte* Movva,

ness, all cases properly focus on the method of "translation" in their inquiry.

In *Amgen v. Chugai*,[133] the plaintiff sued for infringement of a patent covering the natural DNA sequence encoding for human erythropoietin (EPO). The defendant asserted, among other defenses, that Amgen's patent was invalid under 35 U.S.C. § 103. Although the Federal Circuit found that it was "obvious to try" to obtain the DNA sequence of erythropoietin following probing methods available at the time, it also considered that the latter did not enable the inventor to do so with a "reasonable expectation of success."[134] In other words, the applicant had used a nonobvious improvement to the prior art method to find the DNA sequence. The only improvement the court could find was that Amgen's inventor had used a known method under more painstaking conditions than been previously done[135]. To retrieve the DNA coding for erythropoietin, the inventor had used two fully degenerated sets of DNA probes to screen a genomic DNA library, whereas the same had only been done before with cDNA libraries, which are easier to screen due to a smaller size. The court stated:

> The district court specifically found that, as of 1983, none of the prior art references "suggest[s] that the probing strategy of using two fully-redundant [sic] sets of probes, of relatively high degeneracy [sic], to screen a human genomic library would be likely to succeed in pulling out the gene of interest." While it found that defendants had shown that these procedures were "obvious to try," the references did not show that there was a reasonable expectation of success.
>
> We agree with the district court's conclusion, which was supported by adequate testimony.[136]

As a result, the DNA was found nonobvious and the patent valid. The extreme care the Federal Circuit took to demonstrate that the prior art probing method was indeed not enabling in order to ultimately admit the validity of Amgen's patent illustrates the growing

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31 U.S.P.Q.2d (Bd. Pat. App. & Int. BNA) 1027, 1033 (Bd. Pat. App. & Int. 1993); *In re* Sun, 31 U.S.P.Q.2d (BNA) 1451, 1454 (Fed. Cir. 1993).

133. 927 F.2d 1200 (Fed. Cir. 1991).

134. The court found not enabling both a first approach using two sets of fully degenerate synthetic probes deduced from the partial human erythropoietin amino acid sequence, and a second approach using as probe a baboon gene with known homology to the human gene *Id.* at 1208.

135. 927 F.2d 1200 at 1207-1208 (Fed. Cir. 1991).

136. *Id.* (citations omitted).

tension between the statutory requirement for nonobviousness, which appears especially challenging for biotechnology inventions, and the policy concern that patent protection is necessary for biotechnology products that may potentially be developed into drugs.

Two years later, *In re Bell*[137] addressed a patent application directed to DNAs encoding human insulin-like growth factors (IGF). The application was first rejected by the PTO Board on grounds of obviousness over the prior art disclosure of IGF's amino acid sequences and prior art probing methods. The Federal Circuit reversed, first noting that due to the degeneracy of the genetic code, the amino acid sequence of IGF by itself could not render the gene obvious. It also found that the prior art retrieval method which was used could not fill the gap[138] because it taught away from the method used by the applicant.[139]

By focusing specifically on a particular method,[140] which arguably taught away from the invention, the Federal Circuit avoided a discussion of the more general prior art probing method the applicants had actually used. Had it done so, it would probably have had to find obviousness since the general method was actually enabling, i.e., able to retrieve the DNA with a reasonable expectation of success. The court likely believed that the patentability argument that DNA retrieval methods were not "enabling" was growing weaker as the technique improved. Distancing itself from that type of argument, the court insisted at the very end of its decision that the focus on the retrieval method was misplaced because the applicant had claimed a product, not a method.[141] Most of the court's analysis nevertheless focused on the retrieval method.[142] It is not surprising, given the various traditional criteria able to rebut an obviousness finding (lack of suggestion, lack of enabling method, unexpected properties), that the lack of an enabling method is the only one which makes sense in the context of translation DNAs.

Other decisions, by both the Federal Circuit and the PTO Board, use the same focus on the method but decide for obviousness. In *Ex parte Hudson*,[143] the PTO Board had to decide the patentability of a

137. *In re* Bell, 991 F.2d 781 (Fed. Cir. 1993).

138. This gap was referred to above as the "information gap" when one goes from protein to DNA.

139. Sherman M. Weissman, *Method for Cloning Genes*, U.S. Pat. No. 4,394,443.

140. The method was first described by Weissman, who patented it. *See id.*

141. *Bell*, 991 F.2d at 785.

142. *Id.*

143. 18 U.S.P.Q.2d (BNA) 1322 (Bd. Pat. App & Int. 1990).

gene encoding a porcine protein (preprorelaxine). The partial amino acid sequence of preprorelaxine was previously known, and its existence as a subunit structure suggested. The Board essentially held that both suggestion in the prior art and a reasonable expectation of success (enabling method) were present, rendering the gene unpatentable based on obviousness:

> [O]nce the amino acid sequence of a known useful protein is known, there is motivation for one of ordinary skill in the relevant art to construct a synthetic gene for biosynthesis of that protein. Whether or not the specific biosynthesis involved would have been obvious under 35 U.S.C. § 103 depends on the specific facts in each case, but the critical inquiry is would there have been a reasonable expectation of success in achieving the desired goal, applying only the knowledge evidenced as being part of the prior art. The weight of the evidence of record here is that there would have been such a reasonable expectation of success[144].

In *Ex parte Deuel,*[145] the PTO Board reached essentially the same conclusion, deciding that the DNA sequence encoding for human heparin-binding growth factor (HBGF) was prima facie obvious from its partial amino acid sequence. It identified the issue at stake as "whether or not knowledge of the partial amino acid sequence of a protein, in conjunction with a reference indicating a general method of cloning, renders the invention as a whole, i.e., the gene, *prima facie* obvious."[146]

The court then went on to consider whether the prior art knowledge of both the N-terminal amino acid sequence of a protein of interest and a method of probing which allowed the isolation of the DNA corresponding to a protein whose N-terminal amino acid sequence is known, would render the retrieval of the DNA feasible with a reasonable expectation of success.[147] Accordingly, it rejected all claims on obviousness grounds.[148] The PTO Board decision was subsequently overturned by the Federal Circuit.[149]

In *Ex parte Movva,*[150] the PTO Board repeated what it had said in *Ex parte Hudson* and *Ex parte Deuel* even though its decision

144. *Id.* at 1324 (citation omitted).
145. 33 U.S.P.Q.2d (BNA) 1445 (Bd. Pat. App. & Int. 1993).
146. *Id.* at 1447.
147. *Id.* at 1448-49.
148. *Id.* at 1450.
149. *In re* Deuel, 51 F.3d 1552 (Fed. Cir. 1995). *See infra* Part III.A.2.
150. 31 U.S.P.Q.2d (BNA) 1027 (Bd. Pat. App. & Int. 1993).

came shortly after the Federal Circuit's decision in *In re Bell.* It deemed the gene coding for swine growth hormone (sGH) obvious from the partial amino acid sequence of sGH, despite the degeneracy of the genetic code. The PTO Board considered that the prior art general method of DNA probing (Suggs) rendered the retrieval of the complete genetic sequence feasible with a reasonable expectation of success. Unlike the court in *Bell,* the PTO Board focused on the general probing method and not on a specific method which could "teach away" from it.

A few months after *Bell,* the Federal Circuit decided a similar issue in *In re Sun.*[151] The PTO Board had rejected an application for a DNA encoding of a plant protein on the basis that two abstracts published more than a year before by the applicants, describing the protein by its properties and physicochemical features, anticipated it and thus rendered it obvious.[152] The applicants having omitted to dispute an inherency finding by the PTO Board, appealed to the Federal Circuit, which examined the case primarily as an anticipation case.[153] Accordingly, its inquiry focused on whether the references cited as anticipating were enabling.[154] The holding is nevertheless relevant, a fortiori, to obviousness analysis. Although neither of the allegedly anticipating abstracts is directly quoted, nor their exact references given, the text of the decision implies that they only give basic information on the protein:

> Although the examiner admitted that the abstracts lacked the "teaching of specific amino acid sequences encoded by the DNA sequences," ... he nevertheless found that all limitations of the claims were inherent in these publications. Appellants did not dispute inherency.
>
> ....
>
> In the final office action, the examiner took official notice of the availability to one skilled in the art of "protein purification and sequencing techniques, molecular weight determination techniques, sedimentation rate determination techniques, oligonucleotide synthesis techniques, DNA isolation techniques, mRNA isolation techniques, cDNA synthesis techniques, and hybridization techniques."[155] The examiner further noted that "[n]o evidence of the

151. *In re* Sun, 31 U.S.P.Q.2d (BNA) 1451 (Fed. Cir. 1993).

152. *Id.* at 1453

153. *Id.* at 1455.

154. *Id.*

155. Interestingly, the PTO Board took the exact opposite position in *Ex parte* Maizel,

> recalcitrance of the... [specific]... protein to conventional protein purification or sequencing procedures was presented," nor evidence "regarding the recalcitrance of the gene encoding the... [specific]... protein to conventional probing or cloning techniques."
>
> ....
>
> It is undisputed that the publications disclosed the location and characteristics of the relevant... protein. The examiner then took official notice that standard techniques were available for separating proteins, determining sedimentation rates and molecular weight, and determining amino acid sequences. These would enable isolation of the subunit of the protein and determination of its structure. The publications also disclosed that a... DNA fragment... was used as a probe. The examiner asserted that with this description of the probe, one of ordinary skill in the art could use conventional techniques to make the probe, and therefore, to practice the claimed invention.[156]

Since all claims in the application were considered as anticipated, the court did not reach directly the issue of obviousness. Yet, anticipation was based on the finding by the PTO Board that the claims were inherent in the abstracts, which the applicants had not appealed. Had they done so successfully, inherency appears dubious at best. The court would have had to examine the case as an obviousness case. In that event, an obviousness finding would probably have been reached, since all steps of the "translation," from the basic information on the protein provided in the abstracts to the claimed DNA, are clearly described by the court as being "available to one skilled in the art."

The British Court of Appeals took a similar approach in reviewing Genentech's patent on the DNA encoding human tissue

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which was decided about a year before *In re* Sun.

> It is the examiner's position that BCGF is described as a protein useful in bolstering the immune response and the knowledge of the existence of the protein would have motivated one of skill in the art to utilize recombinant DNA protocols to (1) isolate the protein, (2) sequence the protein, (3) construct synthetic probes from the proteins, (4) utilize the probes to isolate messenger RNA, (5) synthetize a cDNA, and (6) produce additional protein. We reverse the rejection. The examiner's position reflects the "obviousness to try" approach of the "armchair" chemist.

Ex parte Maizel, 27 U.S.P.Q.2d (BNA) 1662, 1668 (Bd. Pat. App. & Int. 1992). Unlike the other cases cited, in both *In re* Sun and *Ex parte* Maizel, the "translation" method examined includes the isolation/purification/sequencing of the protein. *Maizel*, 27 U.S.P.Q.2d at 1668; *Sun*, 31 U.S.P.Q. at 1453.

156. *In re* Sun, 31 U.S.P.Q.2d (BNA) 1451 (1993).

plasminogen activator (t-PA).[157] It found the DNA sequence obvious over t-PA itself, which the prior art characterized by its properties and various physicochemical features, but not by its amino acid sequence.[158] Although the British court expressed it in different words than the U.S. courts, it made essentially the same analysis, inquiring into whether the retrieval method used by Genentech's inventor had a reasonable expectation of success:[159]

> Lord Diplock was indeed concerned with obviousness, as Diplock L.J., in the case of Johns-Manville Corp's Patent.... [H]e expressed the view that the case that an allegedly inventive idea was at the priority date "obvious and clearly did not involve any inventive step" would have been made out if before the priority date the man skilled in the art would have thought the idea well worth trying out in order to see whether it would have beneficial results. He took the view that *it would be enough that the person skilled in the art would assess the likelihood of success as sufficient to warrant actual trial, without postulating prior certainty of success.* In Olin Mathieson Chemical Corp v. Biorex Laboratories Ltd, Graham J. formulated the question... as being whether a notional research group at the relevant date *would have been directly led to try a certain idea, in the expectation that it might well produce a useful result. Again certainty of success was not postulated.*
>
> By the various tests set out in the immediately foregoing paragraph it was indeed obvious, in my judgment, to the person skilled in the art to set out to produce human t-PA by recombinant DNA technology.[160]

The split in these decisions on very similar matters is hardly explained by the maturation of the translation technology which would have, from one day to the other, rendered obvious products which were previously patentable. All patent applications described had similar priority dates, which were in the early to mid 1980s. A better explanation would be that the technology effectively matured during

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157. Genentech Inc.'s Patent, [1989] R.P.C. 147 (C.A. 1988). The application also claimed t-PA itself, as well as various methods relating to its manufacture. *Id.*

158. [1989] R.P.C. 147. Like in *In re* Sun and *Ex parte* Maizel, the "translation" method examined in Genetech Inc.'s Patent included the isolation/purification/sequencing of the protein or part of it (here t-PA). *Id.*

159. English patent law uses the terms "inventiveness" or "inventive step" rather than "nonobviousness." Notwithstanding the variation of the terminology, the underlying notion is similar.

160. Genentech Inc.'s Patent [1989] R.P.C. at 242 (emphasis added).

this period, but this fact was not acknowledged simultaneously by the various courts or authorities making the relevant decisions.

An alternative explanation of the split decisions is that the decisions split according to their respective deciding authorities. Both cases concluding nonobviousness and patentability were decided by the Federal Circuit;[161] whereas most cases concluding the opposite originate from the PTO Board.[162] Kenneth Burchfiel distinguishes a "PTO analysis of biotechnology claims," differing from that of the Federal Circuit.[163] However, in all cases cited herein, the fundamental approach to obviousness analysis taken by both the Federal Circuit and the PTO is the same: focus on whether or not the method used to obtain the DNA has a reasonable expectation of success. The Federal Circuit is more inclined than the PTO to decide that there is no reasonable expectation of success in using the method, which probably reflects a more "pro-patent" attitude from the Federal Circuit as contrasted to that of the PTO.[164] However, in an era where the translation method at the heart of the inventions is practiced daily by innumerable scientists worldwide, the Federal Circuit could not keep rendering nonobviousness decisions by using the same obviousness analysis. In addition, the advent of the Human Genome Project and related extensive genomic databases will soon render this position even less sustainable since the translation step, considered until now as the main bottleneck in the process of retrieving genes, will become considerably simpler.[165] The tension between the statutory requirements for patentability and the policy concern that patent protection is necessary had reached a breaking point.

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161. Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200 (Fed. Cir. 1991); *In re* Bell, 991 F.2d 78 (Fed. Cir. 1993).

162. *Ex parte* Hudson, 18 U.S.P.Q.2d (BNA) 1322 (Bd. Pat. App. & Int. 1990); *Ex parte* Movva, 31 U.S.P.Q.2d (BNA) 1027 (Bd. Pat. App. & Int. 1993); *Ex parte* Deuel, 33 U.S.P.Q.2d (BNA) 1445 (Bd. Pat. App. & Int. 1993).

163. KENNETH J. BURCHFIEL, BIOTECHNOLOGY AND THE FEDERAL CIRCUIT 86 (1995).

164. The Court of Appeals for the Federal Circuit was created in 1982, coinciding with a radical change in U.S. government policy toward intellectual property rights. This ended decades of weak patent enforcement and strong antitrust policy. The new patent policy was notably implemented by the Stevenson-Wydler Act and the Bay-Dohl Act, both enacted in 1980. Both acts encourage technology transfer from the public to the private sector. 15 U.S.C. §§ 3701-3714 (1988); 35 U.S.C. §§ 200-211 (1988).

165. Instead of having to screen innumerable clones for probe hybridization at the lab bench (in the case of erythropoietin, Amgen had to probe 1,500,000 phage plaques of human genomic library with its sets of degenerated probes), one will be able to "virtually" hybridize "virtual" degenerate probes to "virtual" clones simply by comparing the DNA probe sequence information deduced from the protein sequence to the sequence information stored in computer databases.

Faced with this dilemma and pressured by the biotechnology industry,[166] the Federal Circuit chose to maintain the patentability of "translation" DNAs by overruling the PTO in *In re* Deuel.[167] To reach its decision, the court radically changed its approach to the obviousness analysis. This article will now briefly discuss the important shortcomings of this decision.[168]

2. *In re Deuel*

The court first decided that the approach it had taken in *Amgen v. Chugai* and *In re Bell,* i.e., focusing on the reasonable expectation of success of the retrieval method, was improper. It forcefully repeated the statement it had made in *In re Bell* without following it:

> We today reaffirm the principle, stated in Bell, that the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question of whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs.[169]

In spite of its superficial appeal, this position overlooks an important aspect of translation DNAs: they are essentially naturally-occurring products, in contrast to created or partly created structures. Most of the contribution of the inventor resides in discovering the translation DNA. Accordingly, the obviousness inquiry in such products must necessarily focus on the retrieval method; adopting another position amounts to deciding that they are by definition non-obvious or that § 103 does not apply to them.[170] Most difficulties arise because biotechnology is the first technology in history which allows one to make discoveries in a reliable and systematic way once some basic information is provided (e.g., an amino acid sequence).

Instead of acknowledging the specificity of the technology involved, the court focused on a criterion familiar to old time chemists whose main way to design new compounds was molecular modification — structural similarity.

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166. See the Amicus Brief of the Biotechnology Industry Association and the Bay Area Bioscience Center urging the Federal Circuit to reverse the PTO's decision in *Ex parte* Deuel.

167. *In re* Deuel, 51 F.3d 1552, 1560 (Fed. Cir. 1995).

168. *See also* Philippe Ducor, *The Federal Circuit and In re Deuel: Does § 103 Apply to Naturally Occurring DNA?*, 77 J. PAT. & TRADEMARK OFF. SOC'Y 871 (1995).

169. *In re* Deuel, 51 F.3d 1552, 1559 (Fed. Cir. 1995).

170. Although the debate on the patentability of "products of nature" is now largely obsolete, doctrine and jurisprudence having decided long ago that they are patentable under some conditions. It does not mean that these types of discoveries (as opposed to man-created structures) have no consequence in patent law.

> Because *Deuel* claims new chemical entities in structural terms, a prima facie case of unpatentability requires that the teachings of the prior art suggest the claimed compounds to a person of ordinary skill in the art. Normally, a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds.[171]

Although the use of the conditional "may" opened up the possibility that elements other than structural similarity might be relevant to the obviousness determination,[172] the court acts as if this were not the case:

> Here, the prior art does not disclose any relevant cDNA molecules, let alone close relatives of the specific, structurally-defined cDNA molecules of claims 5 and 7 that might render them obvious .... [W]hile the general idea of the claimed molecules, their function, and their general chemical nature may have been obvious from [the prior art] teachings, and the knowledge that some gene existed may have been clear, the precise cDNA molecules [claimed] would not have been obvious over the [prior art], because [the prior art] teaches proteins, not the claimed or closely related cDNA molecules.[173]

Structural similarity makes little sense in the context of informational molecules such as DNAs, which are not designed by molecular modification.[174] An interesting implication of using this criterion in the context of "translation" DNAs (or other naturally

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171. *In re* Deuel, 51 F.3d 1552, 1557-58 (Fed. Cir. 1995).

172. Such as the informational similarity existing between a protein and its corresponding DNA.

173. *In re* Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995).

174. The attachment to the notion of structural similarity as the only element ever able to render a compound obvious and the related implication that new compounds are still made by molecular modification can also be found in Kenneth Burchfiel's book. Criticizing the position of the PTO, he describes it as being "that enablement of an invention by prior art disclosure of a similar method is sufficient to establish the obviousness of a biotechnology product claim to the particular nucleic acid sequences obtained, *without consideration of the relationship of the prior art structures to the claimed structures, or the motivation provided by the prior art to make the required modifications.*" BURCHFIEL, *supra* note 50 at 88 (emphasis added).

Similarly, acknowledging the Federal Circuit's decision with satisfaction, Chester A. Bisbee writes "the message sent down from the CAFC is now clearly that biotechnology is to be looked at as a subdivision of chemical patent practice." Chester A. Bisbee, *Novel Gene Sequence Discovery Ruled Not Obvious,* GENETIC ENGINEERING NEWS, June 1, 1995, at 12.

occurring products) is that it is virtually never met. This amounts to a practical elimination of the requirement for nonobviousness for these products, even when all the information necessary to discover them is previously available.

On the same page that the court states that proteins could in no way render obvious the corresponding DNA sequences, it directly contradicts itself by acknowledging they indeed can, when encoded by "unique" codons:[175] "A different result might pertain, however, if there were prior art, e.g., a protein of sufficiently small size and simplicity, so that lacking redundancy, each possible DNA would be obvious over the protein."[176]

By this statement, the court implicitly admits that the informational similarity of structurally different compounds — protein and corresponding DNA — is as relevant to the obviousness determination as the structural similarity between other compounds. This is because both actually suggest the new product to a person skilled in the art.

In contrast, the court clearly rejects this notion when the prior art protein is constituted from amino acids encoded by multiple codons on the basis that contemplation or conception of the DNA is impossible:[177]

> The redundancy of the genetic code precluded contemplation of or focus on the specific cDNA molecules of claims 5 and 7. Thus, one could not have conceived the subject matter of claims 5 and 7 based on the teachings in the cited prior art because, until the claimed molecules were actually isolated and purified, it would have been highly unlikely for one of ordinary skill in the art to contemplate what was ultimately obtained. What cannot be contemplated or conceived cannot be obvious.
>
> . . . .
>
> [K]nowledge of a protein does not give one a conception of a particular DNA encoding it.[178]

The argument has some superficial merit. One cannot effec-

175. The term "unique" refers to an amino acid coded for by a single codon. Only two amino acids (methionine and tryptophane) are specified by such a unique codon.

176. *In re* Deuel, 51 F.3d 1552, 1559 (Fed. Cir. 1995). The use of the term "each" is probably inadvertent, since the purpose of the example is that only one DNA can possibly encode the protein.

177. The same is true when the prior art contains only a partial amino acid sequence. *See id.* at 1558-59.

178. *Id.*

tively say that a protein encoded by multiple possible DNAs has an "identical informational content" to its native DNA. Due to the redundancy of the genetic code, some information is lost during the translation process. A prior protein does not give direct, immediate conception of its native DNA. However, the prior art contains more than only the protein. It also contains various gDNA and cDNA libraries (and databases), disclosing scores of natural genomic or expressed DNAs. Thanks to such libraries, one skilled in the art can reliably fill the informational gap between a protein and its native DNA.[179] Hence, while it is true that knowledge of a protein sequence does not give one a *direct* and *immediate* conception of the corresponding native DNA by mere mental processing and without any experimentation,[180] it is not true that a DNA cannot *possibly* be contemplated or conceived from its corresponding protein sequence. All it takes is a routine hybridization procedure, soon simplified to a nearly instantaneous computer search.

Accordingly, the issue in determining obviousness becomes whether "suggestion in the prior art" requires that the conception of the new invention be *direct* and *immediate* from the prior art. The court seems to imply the requirement of direct and immediate when it states, "What cannot be contemplated or conceived cannot be obvious."[181] However, obviousness has never required that the new invention be conceived without the slightest testing or experimentation. All obviousness requires is a reasonable expectation of success.[182] Even the enablement requirement of § 112, relating to inventions already made, prohibits only *undue* experimentation. Hence, the court seems to require that the prior art disclose the new invention in a more than enabling way, before deeming it patentably obvious. This is certainly not the intent behind § 103. This is, rather, the rationale behind § 102 on novelty.

The clearest evidence of the confusion in the court's reasoning

179. It also fills the gap between incomplete and complete amino acid sequences, since hybridization can occur unambiguously with partial sequences. The minimal size for probes is typically 15 to 25 residues (15 to 25-mers oligonucleotides), depending on the size of the library screened.

180. For example, expressed as a formula on a paper.

181. *In re* Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995).

182. *See In re* O'Farrell, 853 F.2d 894, 904 (Fed. Cir. 1988) ("For obviousness under §103, all that is required is a reasonable expectation of success."); *See also* Amgen Inc., v. Chugai Pharmaceutical Co., 927 F.2d 1200 (Fed. Cir. 1989); *In re* Sun, 31 U.S.P.Q.2d (BNA) 1451 (Fed. Cir. 1993). In the chemical field, see *In re* Dow Chem. Co., 837 F.2d 469 (Fed. Cir. 1988) and *In re* Longi, 759 F.2d 887 (Fed. Cir. 1985).

is probably the use, in an obviousness context, of the term and notion of "conception." Under U.S. law, conception is part of the determination of who among two or more independent inventors deserves the patent for a single invention. The patent is granted to the first to conceive the invention, provided he is subsequently diligent in reducing it to practice.[183] Accordingly, conception is an important notion for establishing priority in interference proceedings.[184]

However, conception has nothing to do with obviousness, unless one wants to equate the latter with novelty. In the DNA field, conception occurs only at the same time as reduction to practice, or full invention of the claimed DNA.[185] Conception helps in deciding who among several inventors is the first to invent a DNA. Conception does not help in deciding what is the minimal distance between the prior art and a new invention necessary to make it nonobvious and patentable. Accordingly, unlike conception, obviousness of a DNA does not require that the prior art fully discloses it. The very use of the notion of "reasonable expectation of success" in obviousness determinations confirms that point, allowing for some initial uncertainty in the actual conception/reduction to practice of an obvious invention.

By confusing obviousness and conception, the court implies that obviousness does indeed require an absolute expectation of success. It also decides that a DNA not yet invented cannot be obvious. Both positions are clearly erroneous.

Beyond merely legalistic arguments, the best proof that translation DNAs are currently obvious to those skilled in the art is evidenced by the researchers' very attitudes. Today, if a researcher discovers a new protein and its probable properties, he usually will not publicize the information until he has found the corresponding gene. To explain this behavior in a community whose motto is "publish or perish," one must realize that it would be obvious to another research team to pick up the information and clone the gene.

Whatever its legal or logical flaws, *In re Deuel* is currently the

183. 35 U.S.C. § 102(g) (1988). The United States has a first-to-invent system for priority, in contrast to the rest of the developed world, which has a first-to-file system. Unlike the patent term which was extended to 20 years from the date of filing, the first-to-invent system has not yet been changed to a first-to-file system as a result of the U.S. GATT negotiations.

184. Due to its first-to-invent system, U.S. law provides a procedure directed to resolving patent "interferences", i.e., determining whom of two alleged inventors is actually the first to invent the claimed subject matter and deserves the patent.

185. *See* Fiers v. Revel, 984 F.2d 1164, 1168-69 (Fed. Cir. 1993). *See also* Fiddes v. Baird, 30 U.S.P.Q.2d (BNA) 1481, 1483 (Bd. Pat. App. & Int. 1993).

law. One should nevertheless be conscious that this decision is more consistent with the pro-patent stance of the Federal Circuit and the interests of the industry, rather than with established patent law.[186]

B. *"Molecular Modification": Second Generation Proteins and DNAs*

The second category of recombinant inventions concerns DNAs or proteins obtained by molecular modification, hence involving a conception process most similar to traditional chemistry. As in traditional chemistry, the principle is to start from a prior art molecule and modify it incrementally until some advantageous property is found. Instead of small organic molecules, the starting material is a protein or a DNA sequence.[187] Instead of substituting chemical radicals (adding or subtracting) the molecular modification of proteins (or DNAs) involves substituting (adding or subtracting) one or more amino acids (or nucleotides). Even though amino acids or nucleotides are bigger "building blocks" than typical chemical radicals, proteins and DNAs are also bigger when compared to typical chemical compounds. As a result, the modifications can still be considered "incremental" while preserving the underlying presumption that similar compounds have similar properties in the context of proteins and DNAs.[188] In addition, similar to chemical radicals, amino acids or nucleotides have by themselves no independent meaning or function outside the context of the macromolecule. As a result, the effect of their substitution, addition, or subtraction on the properties of the modified molecule (second generation protein) cannot be predicted. It follows that if any advantageous property arises from the modification, it will be an unexpected property or result which can be prop-

186. Those close to the industry reacted cheerfully to the Federal Circuit decision. *See, e.g.*, Bisbee, *supra* note 174, at 1, 12. *See also* Special Panel Discussion (Bay Area Bioscience Center), The Implications of *In re* Deuel: Patenting Genes Made Easier, A Win for the Biotech Industry? (April 18, 1995).

187. Since ultimate properties lie more often in proteins than DNAs, the material directly undergoing molecular modification will often be a protein.

188. "[M]any of the amino acids in proteins are not essential, and when they are replaced by somewhat similar amino acids, the proteins often retain full activity." JAMES D. WATSON ET AL., MOLECULAR BIOLOGY OF THE GENE 436 (4th ed. 1987). This does not mean that the presumption ultimately proves valid in all cases. Substituting only one amino acid in a protein can have dramatic consequences (e.g., substitution of Val for Glu at position 6 of the ß-globin chain in haemoglobin causes sickle cell anemia). The same is also true from smaller molecules (e.g., closely related opiates molecules have agonist or antagonist effects). If the presumption was always valid, no compound obtained by molecular modification could ever be patentable because its properties would never be "unexpected" under *In re Papesch*, 315 F.2d 381 (C.C.P.A. 1963).

erly used to rebut the prima facie obviousness case based on structural similarity.

As a result, the obviousness analysis developed for traditional chemistry case law applies without major problems to second generation proteins (DNAs) obtained by molecular modification.

If one follows the pattern described above for determining obviousness in traditional chemicals, one can see that second generation proteins[189] obtained by molecular modification of prior art proteins will often be found prima facie obvious. Along the lines of *Hass-Henze,*[190] second generation proteins will generally be considered as structurally similar to the prior art protein from which they are derived by incremental amino acid modifications. Since the prior art protein will often have some *in vivo* property, according to *Stemninsky-Dillon,*[191] it will constitute a sufficient general suggestion or motivation to make minor modifications leading to the second generation protein. Site-directed mutagenesis or, alternatively, total chemical synthesis certainly constitutes enabling methods of making second generation proteins along the lines of *In re Hoeksema.*[192] As a result, second generation proteins will generally be found prima facie obvious. However, for the reasons mentioned above, any significant change in properties from the prior art protein will generally be unexpected in the meaning of *In re Papesch,* giving the applicant an opportunity to rebut the prima facie case of obviousness, and obtain a patent covering the second generation protein.[193] The situation is summarized in Table 3.

189. Except when noted, what is said about second generation proteins is also valid for their encoding DNA.

190. *See supra* Part II.B.1.a (discussing Hass-Henze line of cases).

191. *See supra* Part II.B.1.b (discussing *Stemninsky-Dillon* line of cases).

192. 399 F.2d 269 (C.C.P.A. 1968).

193. When a DNA is claimed instead of the corresponding second generation protein, the properties of the protein itself are indirectly considered as the properties of the DNA. *See Ex parte* Anderson, 30 U.S.P.Q.2d (BNA) 1866 (Bd. Pat. App. & Int. 1994).

TYPE OF INVENTION	STATUTORY DISPOSITION APPLICABLE	INVENTION IS "OBVIOUS TO A SKILLED PERSON" IF PRIOR ART PROVIDES ("PRIMA FACIE" OBVIOUSNESS)	FACTOR USUALLY REDEEMING PATENTABILITY ("PRIMA FACIE" REBUTTAL)
Second generation proteins and DNAs obtained by molecular modification (idem traditional chemical compounds)	35 U.S.C. § 103(a): "A patent may not be obtained . . . if the . . . subject matter . . . would have been obvious to a person having ordinary skill in the art . . . ."	structurally similar compound(s) + motivation to make the new compound (i.e., some useful property in the prior art compound) + enabling disclosure of a method to make the new compound	unexpected properties in the new compound

Table 3. Obviousness of second generation proteins and DNAs (obtained by molecular modification).

The case law on obviousness of second generation proteins or DNAs is consistent with this pattern and shows that the claimed molecules often lack the unexpected properties required to rebut a prima facie obviousness case. *Ex parte Anderson*[194] offers a good illustration of this situation and will be discussed briefly.

The applicant claimed a DNA sequence encoding for mature human interleukin-3 (IL-3), whereas the prior art disclosed another DNA sequence encoding for a similar IL-3. The only difference between the two DNA sequences was the amino acid proline at position 8 of IL-3 — the prior art DNA encoded a serine at the same position. Quoting Watson's textbook,[195] the PTO Board first affirms the validity, in the context of proteins, of the presumption that similar compounds have similar properties:

> [A]s a matter of textbook chemistry, a single variation in the amino acid structure of a protein does not normally change the activity and

194. *Id.*

195. *See supra* note 3.

> function of the protein unless the single variation is in a critical region of the protein. Accordingly, the examiner was technologically correct when she stated that the substitution of any one of the amino acids in the protein chain and the similar substitution of the DNA coding for the amino acid would not normally have been expected to have a significant effect on the activity of the protein.[196]

The PTO Board then considered that a new protein (and its corresponding DNA) differing only by one amino acid (or a DNA codon) can be considered as "structurally similar" to the prior art's protein and DNA:

> When one steps back and views the twisted structure of the protein as a whole, and considering the overall similarity of the protein of the prior art versus that coded for by the DNA claimed herein, . . . and also considers the similarity of the DNA of the prior art versus that claimed herein, the minor change in the chemical configuration or design of the molecule discovered or made by appellants is so negligible that a prima facie case of obviousness exists. In legal parlance, on the record herein appellants' structural modification is *de minimis*.[197]

Noting that the prior art gives sufficient motivation to make variants of IL-3, the Board reaffirmed the requirements for a prima facie obviousness case, citing *In re Dillon:*

> [S]tructural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness . . . the burden (and opportunity) then falls on an applicant to rebut that *prima facie* case.[198]

Finally, the PTO Board found that the applicant had not rebutted the prima facie case, having demonstrated no unexpected properties in his product. Note that for prima facie obviousness rebuttal purposes, the PTO takes into consideration the properties of the protein encoded by the claimed DNA, attributing them to those of the DNA itself:

> In the case before us, appellants are claiming a DNA and the use of that DNA. What is of concern in the consideration of rebuttal evidence are the properties of the DNA itself and/or the product it produces, i.e., the protein it codes for. Appellants have

196. *Id.* at 1868.

197. *Id.*

198. *Id.* (quoting *In re* Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990)).

> not provided evidence that the protein coded for by the claimed DNA is any different from that of the prior art in its chemical properties.[199]

Cases prior to *Ex parte Anderson* reach the same conclusion. In *Ex parte Thim,*[200] the applicant claimed a proinsulin having a C-peptide[201] encompassing only two amino acids, selected from Arg-Lys, Lys-Lys, and Lys-Arg. The prior art disclosed natural proinsulin having a C-peptide encompassing thirty amino acids, proinsulins with a C-peptide as short as two amino acids (Arg-Arg), and the advantage of having a short C-peptide chain for good expression yields. The examiner considered the claimed proinsulin prima facie obvious. In his attempted rebuttal case, the applicant showed that the yield of the claimed proinsulin expressed in yeast was greater than that of the prior art proinsulin. The PTO Board decided that such a difference in yield did not constitute an unexpected property able to rebut the prima facie case of obviousness and rejected the application. *Thim* constitutes an example in biotechnology practice where a difference in degree of a property is considered insufficient to rebut a prima facie case of obviousness.[202]

In *Ex parte Gray,*[203] the applicant claimed human ß-NGF[204] with an additional N-terminal methionyl residue.[205] Having found that ß-NGF itself was part of the prior art, the PTO Board considered that N-met-ß-NGF was structurally similar.[206] Reaffirming the presumption that structurally similar compounds have similar properties, the Board held that methionyl-ß-NGF was prima facie obvious and that the applicant had not rebutted this finding. The Board stated "the mere presence of a single methionyl moiety in a sequence of over

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199. *Ex parte* Anderson, 30 U.S.P.Q.2d (BNA) 1866, 1869 (Bd. Pat. App. & Int. 1994).

200. 22 U.S.P.Q.2d (BNA) 1941 (Bd. Pat. App. & Int. 1991).

201. Human insulin itself is composed of two peptides termed A and B chains, held together by sulfide linkages. It is not produced as such; it is initially produced as a single polypeptide chain called proinsulin, in which chains A and B are connected by a C ("connecting") chain which is excised later during post-translational processes.

202. For equivalent cases in chemical practice, see *In re* Lohr, 317 F.2d 388 (C.C.P.A. 1963); *In re* Lunsford, 357 F.2d 380 (C.C.P.A. 1966); *In re* Wagner, 371 F.2d 877 (C.C.P.A. 1967); *In re* Chupp, 816 F.2d 643 (Fed. Cir. 1987). *See also* discussion *supra* Part II.B.2.

203. 10 U.S.P.Q.2d (BNA) 1922 (Bd. Pat. App. & Int. 1989).

204. NGF means Nerve Growth Factor.

205. A N-terminal methionyl residue is generally the result of recombinant expression systems.

206. *Ex parte* Gray, 10 U.S.P.Q.2d (BNA) 1922, 1925-27 (Bd. Pat. App. & Int. 1989). Gray had also claimed natural ß-NGF, which the PTO Board found alternatively anticipated or obvious from the prior art. *See id.* at 1923.

100 amino acids would not have been expected to alter the properties of the compound in a significant respect, in the absence of evidence of the contrary."[207]

On request for reconsideration, the court stated, "appellants have failed to respond to our finding that the protein containing the terminal methionyl group is substantially identical in structure to that [disclosed by prior art references]."[208]

The same conclusion involving an N-terminal methionyl residue is reached in a European patent application by Monsanto.[209] The applicant claimed a method for increasing bovine milk production by administering recombinant bovine growth hormone (bGH), instead of natural bGH as disclosed by the prior art. The amino acid sequences in both recombinant and natural bGH were identical, except for an additional N-terminal methionyl residue in the recombinant version. The European Patent Office Technical Board of Appeal decided that the claimed method using recombinant bGH involved no inventive step,[210] since its result was reasonably expected. Although the decision deals with a method of using bGH and not directly with bGH as a product, both claimed and prior art methods differ only in the product (bGH) used in the method; accordingly, the conclusions also apply to the product itself.

Another European case, *Biogen*,[211] deals with a new version of α-interferon. Although the decision does not mention how different the claimed IFN-α2 is from the prior art IFN-α1, it clearly states that both DNA sequences were close.[212] Examining the issue further, the Technical Board decided that IFN-α2 represented an inventive step over IFN-α1 because, despite its structural similarity, it had an antiviral activity at least thirty times higher. Explained in terms of U.S. law, this increase in activity would have represented an unexpected property (or a difference in degree of a same property amounting to an unexpected property) sufficient to rebut the prima facie case of

207. *Id.* at 1926.

208. *Id.* at 1928.

209. Monsanto, *Method for improved bovine milk production*, T 249/88, dec. 14 Feb. 1989 (unpublished), *cited in* HANS-RAINER JAENICHEN, THE EUROPEAN PATENT OFFICE'S CASE LAW ON THE PATENTABILITY OF BIOTECHNOLOGY INVENTIONS 118 (1993). *See also* R. Stephen Crespi, *Inventiveness in Biological Chemistry: an International Perspective*, 73 J. PAT & TRADEMARK OFF. SOC'Y 351 (1991) (citing same case).

210. "Inventive step" is the equivalent of nonobviousness in European terminology.

211. Biogen, "alpha-interferons," T 301/87, dec. 16 Feb. 1989, EPOR 190 (1990).

212. *Id.* at 195.

obviousness based on structural similarity.[213]

In addition to minor variations in their amino acid sequence, proteins can also differ by their glycosylation patterns. Because their functional impact is generally negligible at the current level of understanding, different versions of a same protein differing only in the glycosylation pattern are generally treated as "structurally similar." This is so because the presumption that "similar" compounds have similar properties remains valid in this context even with such an extended definition of "structural similarity." Accordingly, the obviousness analysis applied in traditional chemistry applies to proteins having various glycosylation patterns without major problems. Similar to the examples of second generation proteins mentioned previously, they will generally be considered prima facie obvious, unless the applicant rebuts the finding by showing some unexpected property.

Again, the case law shows that demonstrating unexpected properties in differently glycosylated versions of a same protein is usually difficult. In *Ex parte Gray,*[214] the applicant claimed both natural and N-terminal methionyl-NGF. Both were apparently produced using a procaryotic expression system, meaning they had no glycosylation pattern, as opposed to the prior art purified natural NGF. Despite this difference, both were found obvious over the purified NGF.[215] Consistent with the presumption that structurally similar compounds have similar properties, the fact that the unglycosylated NGF retained its properties was not considered "unexpected."[216]

In contrast, in certain circumstances the prior art may rebut the presumption and render any retained properties unexpected. *Ex parte Aggarwal*[217] is such a case. Aggarwal claimed a method of treating tumors in animals by administering recombinant lymphotoxin produced in various expression systems. The prior art disclosed the same method using purified natural lymphotoxins. In spite of other

213. As already noted, the same obviousness issues arise in both European and U.S. law despite some variations in terminology. *See* discussion *supra* Part II.B. and *supra* note 190.

214. 10 U.S.P.Q.2d (BNA) 1922, 1923 (Bd. Pat. App. & Int. 1989).

215. Obvious, or even anticipated by natural NGF. The text of the decision in Ex parte Gray is not clear on the §103 or §102/103 grounds of the rejection. *Ex parte* Gray, 10 U.S.P.Q.2d (BNA) 1922 (Bd. Pat. App. & Int. 1989).

216. The same observation could be made in Monsanto, where the N-terminal-met bGH used in the claimed method was certainly unglycosylated, and the natural bGH used in the prior art method certainly was. *See supra* Part II.B.1.a (discussing structural similarity).

217. 23 U.S.P.Q.2d (BNA) 1334 (Bd. Pat. App. & Int. 1992).

problems,[218] the PTO Board successively examined the obviousness of the claims on methods using recombinant lymphotoxins having various glycosylation patterns. It first decided that the claims related to glycosylated lymphotoxins expressed in eucaryotic systems (human, non-human mammalian, yeast cells) were obvious, because the variations observed in their glycosylation patterns were minor when compared to the glycosylation pattern of the prior art purified protein and would not render the cytotoxic property of the protein unexpected. Conversely, the Board decided that the claims related to the unglycosylated lymphotoxin expressed in procaryotic systems such as *E. coli* were nonobvious, because unlike in *Ex parte Gray,* there were prior art references indicating that the glycosylation pattern played a definite role in the conformation of lymphotoxin and was necessary for its properties. In other words, cytotoxic activity in an unglycosylated lymphotoxin was considered as an unexpected property and therefor would be proper to rebut the prima facie case of obviousness:

> The examiner has requested this Board to follow *Ex parte Gray*, and affirm the examiner's rejection in its entirety. We have followed *Gray*, with regard to the obviousness of using a glycosylated recombinant lymphotoxin for treating tumors. However, this case is distinguishable because, unlike *Gray*, there is evidence of record herein which indicates that the unglycosylated lymphotoxin would not have been expected to retain its cytotoxic activity.[219]

There is no case law in the recombinant field dealing directly with the patentability of a protein or a DNA which shares, in addition to a new and unexpected property, significant common properties with prior art proteins or DNAs. As long as the claimed molecule is structurally similar to prior art compounds (i.e., differ only incrementally), there is no reason to question the applicability of the traditional chemical case law.[220] The prospect is clearly different for the proteins and DNAs described in the next section.[221]

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218. The application was primarily rejected on 35 U.S.C. § 101 (1988) and 35 U.S.C. §112 (1988) grounds.

219. *Ex parte* Aggarwal, 23 U.S.P.Q.2d (BNA) 1334, 1337 (Bd. Pat. App. & Int. 1992).

220. See *In re* De Montmollin, 344 F.2d 976 (C.C.P.A. 1965); *In re* Mod, 408 F.2d 1055 (C.C.P.A. 1969); *In re* Albrecht, 514 F.2d 1385 (C.C.P.A. 1975); *In re* May, 574 F.2d 1082 (C.C.P.A. 1978). *See also* discussion *supra* Part II.B.2.b.

221. Ignoring the distinction made here between "molecular modification" and "combination" macromolecular inventions, an author points out the difficulties in applying the "balancing" doctrine for common properties. However, his objection is valid only for

Another type of "second generation" protein and DNA can be designed by a very different process. Instead of substituting (adding, or subtracting) per se meaningless amino acids or glycosylation patterns prior art proteins or substituting nucleotides to prior art DNAs, these proteins and DNAs are designed by substituting (adding or subtracting) functional domains.[222] Such "second generation" proteins and DNAs will be considered as "combination" inventions and discussed in the following section.

C "Combination" Inventions: DNA Vectors and Second Generation Proteins/DNAs Combining Heterogeneous Functional Domains

Both traditionally designed chemical compounds and second generation DNAs or proteins described in the preceding section are conceived by the same approach: incremental molecular modification of prior art compounds. In such cases, the substituted, added, or subtracted chemical elements are proportionately small, and the modified molecule preserves the general structure of the starting molecule. As a result, the structures of both products are similar, and chances are that their properties are similar as well. Given this presumption, any significant change in properties in the resulting product will be unexpected, and hence apt to rebut a prima facie obviousness finding based on structural similarity.

Even though they can ultimately change the properties of the whole compound dramatically, the chemical elements substituted, added, or subtracted in traditional molecular modification have no autonomous significance or function. The advent of biotechnology in general, and of recombinant technology specifically, has enabled the scientist to substitute, add, or subtract bigger chemical elements having a known autonomous function or meaning. DNA regulatory sequences and partial amino acid sequences recognized as functional domains or epitopes are examples of such elements. The contribution of the inventor to such "combination" macromolecules resides in the very combination of prior art functional elements directed toward a specific purpose and not in the nearly blind modification of a prior art chemical formula. In this context, and in contrast to the traditional molecular modification approach, the designer does not generally

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"combination" inventions. Sean Johnston, *Patent Protection for the Protein Products of Recombinant DNA*, 4 HIGH TECH. L.J. 249, 263 (1989).

222. Or other amino acid or nucleotide sequences known to be responsible for some property independent of the macromolecule in which they are ultimately integrated. A functional domain is a region of a protein, known for performing some basic function of the protein.

need to carry out experiments in order to discover the potential new and unexpected properties of its product. Rather, because the prior art chemical elements he substitutes, adds, or subtracts have an autonomous significance, the inventor can directly envision what structure he should give to his invention to confer upon it the properties which will resolve the specific problem he has in mind. Accordingly, the conferred properties will by definition not be unexpected, and will offer no remedy in case the combination invention is found prima facie obvious by the PTO.

In this respect, inventors of "combination macromolecules" are in a situation comparable to that of inventors of mechanical devices, where most inventions are combinations of prior art elements, and precisely designed *ex ante* to bear the properties able to resolve a specific problem — function precedes structure. Despite the often repeated stance that biotechnology products are only chemical compounds, "combination macromolecules" arguably represent the point (on the size rule) where reasoning along the lines of mechanical inventions becomes more sensible than reasoning along the lines of traditional chemical inventions. The fact that biotechnology is, for historical reasons, linked more closely to chemistry than to mechanics should not matter. Any tangible matter could ultimately be viewed as a "chemical compound," mechanical inventions included. The relevant point for obviousness analysis is that such inventions involve the combination of meaningful operating elements from the prior art, in contrast to the (nearly) blind substitution, addition or subtraction of per se meaningless radicals. While the contribution of the inventor to a molecular modification invention resides in creating some part of an amino acid or nucleotide sequence or of a chemical formula, the contribution of the inventor of combination macromolecules resides in the specific combination of old elements, each having an independent significance or function and directed to solve a specific problem.[223]

In this context, the criteria developed in traditional chemistry to establish suggestion or motivation in the prior art (structural similarity as in *Hass-Henze* plus known property in the prior art from *Stemninsky-Dillon*) make little sense.[224] For the purpose of obvious-

223. Even the terminology used by those skilled in the field - plasmid or vector *construction* - seems to confirm the analogy with mechanical inventions. No chemist synthesizing new compounds by molecular modification would ever use the same term.

224. Suggestion or motivation is intended here in its broader sense. *See* discussion *supra* Part. II.B.1.b.

ness determination, comparing the chemical structure of two plasmid vectors bearing different functional elements makes no more sense than comparing the chemical structure of two types of can openers. Accordingly, instead of the traditional structural similarity inquiry which leads to absurd results in this context, the same test used in mechanical inventions combining old elements should be adopted for combination macromolecule inventions. As already mentioned, since 1982, the Federal Circuit has considerably clarified the test for determining obviousness in inventions combining old elements. Completely dismissing the Supreme Court's "synergistic results" rule, the Federal Circuit requires that for a combination invention to be obvious, the suggestion or motivation to make the specific combination must be found in the prior art.[225] Although the suggestion does not need to be express or specific,[226] it certainly must go beyond the general suggestion provided in traditional chemistry by the mere knowledge of a property in a structural analog, as spelled out in the *Heinz-Henze* and *Stemninsky-Dillon* line of cases. Robert Harmon adequately summarizes the position of the Federal Circuit about inventions combining old elements. Citing a long line of cases,[227] he writes: "There must be something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination."[228] Indeed, the most powerful (and most frequently used) argument to obtain a patent on a combination invention is to show that the prior art does not provide suggestion or motivation to make the combination.

Lindemann Maschinenfabrik GmbH v. American Hoist and Derrick Company[229] provides a good example, in the mechanical field, of the Federal Circuit's position regarding combination inventions. The patent was directed to a hydraulic scrap shear which was able to process "rigidly massive" scrap metal. Unlike prior art devices, the shear featured two rams on different working surfaces. When light

225. *See supra* Part I.B.1.b.

226. *See* Cable Elec. Prods., Inc. v. Genmark, Inc., 770 F.2d 1015, 1025 (Fed. Cir. 1985). *See also* the concurring opinion of Chief Judge Nies in *In re* Oetiker, 977 F.2d 1443 (Fed. Cir. 1992). In biotechnology, the Federal Circuit seems to require greater specificity in the prior art suggestion of the combination than in other fields. *In re* Vaeck, 947 F.2d 488 (Fed. Cir. 1991). *See also In re* O'Farrell, 853 F.2d 894 (Fed. Cir. 1988) and *In re* Nunberg, 40 F.3d 1250 (1994).

227. *See In re* Geiger, 815 F.2d 686 (Fed. Cir. 1987); Lindemann Maschinenfabrik GmbH v. American Hoist and Derrick Co., 730 F.2d 1452 (Fed. Cir. 1984).

228. ROBERT L. HARMON, PATENTS AND THE FEDERAL CIRCUIT 108 (2d ed.1991).

229. 730 F.2d 1452 (Fed. Cir. 1984).

scrap was fed into the machine, both rams would advance together to crush and compact the scrap. However, when rigid scrap was fed, the two rams were quickly brought to a standstill by the scrap's resistance; the smaller ram then operated independently of the main ram, crushing the rigid scrap with greater force thanks to its smaller surface. In a suit brought for infringement of the patent covering the shear, the defendant asserted that the patent was invalid for obviousness. The district court agreed, finding both small-ram and large-ram machines in the prior art:

> Plaintiff simply put the two features in the same machine and connected them as was necessary depending on whether the scrap was small or large. It used a known connection idea. The '315 [patented] machine possessed one known feature to operate in a known way to produce a known result to deal with the first scrap situation and another known feature operating in a known manner to produce a known result to deal with the second. Clearly, this was an obvious solution using already appreciated or obvious features to solve the problem of how to develop a machine that could handle both types of scrap most economically.[230]

The Federal Circuit reversed, insisting that the combination itself must be suggested in the prior art:

> The '315 patent specifically stated that it disclosed and claimed a combination of features previously used in two separate devices. That fact alone is not fatal to patentability. The claimed invention must be considered as a whole, and the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. That question must here be answered in the negative.[231]

When the prior art does provide adequate suggestion to make the combination, an additional factor might still render the combination nonobvious. The absence of an enabling method for producing the invention can redeem nonobviousness and patentability, as seen in *In re Hoeksema*.[232] However, the argument will rarely apply to molecular combination inventions, since enabling methods for making both plasmids and composite proteins are now generally available.[233]

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230. *Id.* at 1460.

231. *Id.*

232. 399 F.2d 269, 274 (C.C.P.A. 1968). *See* discussion *supra* Part II.B.1.c.

233. Plasmid construction by using restriction enzymes (enzymes that break DNA molecules at specific nucleotide sequences) is now a mature technique. Similar methods can be used to engineer the encoding DNA of a combination protein. Note that "enabling method" is understood here as a method allowing one to obtain the wanted structure, independent of its

As to the notion of unexpected properties, so useful to rebut prima facie obviousness in traditional chemistry and second generation proteins, it has already been noted that it offers little help in combination inventions designed from inception to have definite properties and solve a specific problem. For example, a mechanical device combining several prior art mechanical elements will rarely have unexpected properties or results, since it was designed precisely to have properties able to perform a specific task. The same is true for combination macromolecules.[234] The treatment of recombinant combination inventions is summarized in Table 4:

TYPE OF INVENTION	STATUTORY DISPOSITION APPLICABLE	INVENTION IS "OBVIOUS TO A SKILLED PERSON" IF PRIOR ART PROVIDES	FACTOR USUALLY REDEEMING PATENTABILITY
Combination inventions (mechanical and recombinant combination inventions)	35 U.S.C. §103(a): "A patent may not be obtained . . . if the . . . subject matter . . . would have been obvious to a person having ordinary skill in the art . . . . "	all elements of the combination + suggestion to make the combination	no adequate suggestion to make the combination or no reasonable expectation of success

Table 4. Obviousness of combination inventions.

The available case law concerning macromolecular combination inventions confirms this analysis, focusing both on the prior art motivation to make the combination and on the reasonable expectation of success in practicing the invention.

In 1988, the Federal Circuit decided *In re O'Farrell,*[235] a landmark case on obviousness in biotechnology. The applicant claimed a method of producing proteins in bacteria using a new plasmid.[236] The

ultimate properties.

234. Admittedly, because the understanding of intracellular events is not absolute, there is more room for "unexpected properties" in combination macromolecules than in mechanics. However, the current case law concerning combinations macromolecules never mention "unexpected properties". This tends to confirm the view exposed here that the properties of combination macromolecules are by definition not "unexpected".

235. 853 F.2d 894 (Fed. Cir. 1988).

236. The decision in *In re* O'Farrell only mentions a method, despite the title of the patent

latter combined homologous regulatory DNA sequences, a portion of a homologous gene expressed under the control of the homologous regulatory sequences and lacking the normal gene termination signal, and a heterologous DNA sequence encoding for a protein of interest. The homologous regulatory sequences were intended to control the production of the heterologous protein. A paper describing early results of the applicant's research team was published more than one year before the patent application, constituting prior art.[237] Using the same strategy as the claimed method (linking a foreign gene to a highly regulated indigenous gene), the experiment described in the anticipating paper expressed an aberrant protein resulting from the expression of a ribosomal DNA,[238] instead of a normally expressed protein as described in the patent application. The paper explicitly mentioned the interest of using a functional eukaryotic gene for protein expression, instead of the ribosomal DNA. The court found the invention obvious from the reference; the court observed that "the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art . . . ."[239]

In other words, the reference suggested combining the elements of the invention. As a result, the "suggestion test" described above for combination inventions was met. Answering to the applicant's contention that it had used an improper "obvious to try" standard, the court then held that the prior art not only suggested the specific combination invention but also provided evidence that it would be reasonably successful.[240] Observing that obviousness does not require absolute predictability of success, the court said that the applicants had a reasonable expectation of success in practicing their invention, which rendered the latter obvious from the prior art reference.[241]

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application: "Method and Hybrid Vector for Regulating Translation of Heterologous DNA in Bacteria." However, the issues are identical for both the method and the vector itself. This is confirmed by the decisions T 0292/85 and T 0293/85 of the European Patent Office Technical Board of Appeal, concerning equivalent applications, respectively claiming the method and the vectors claimed in *In re* O'Farrell.

237. 35 U.S.C. § 102(b): "A person shall be entitled to a patent unless . . . the invention was patented or described in a printed publication ... more than one year prior to the date of the application . . . ." 35 U.S.C. § 102(b) (1988).

238. Ribosomes are subcellular components involved in the translation of RNA into proteins. They are themselves composed of proteins and RNA, called ribosomal RNA (rRNA). Accordingly, this rRNA is not intended to be translated into protein, like mRNA's. In the experiment reported in the prior art paper, a DNA encoding for a ribosomal RNA was used to lead to the expression of an aberrant protein.

239. *In re* O'Farrell, 853 F.2d 894, 901 (Fed. Cir. 1988).

240. *Id.* at 902.

241. *Id.* at 903.

Interestingly, the very same application, encompassing the same prior art, went before the European Patent Office Technical Board of Appeal and was judged nonobvious and patentable.[242] The European Board based its decision on two limitations of the claims, which were also present in the claims before the USPTO. The first limitation insisted on a proper reading frame for the inserted heterologous gene, and the second mentioned a sufficient size for the expressed protein in order to avoid proteolytic degradation. None of these limitations were mentioned in the anticipating reference, since it used a ribosomal gene normally not translated into protein after transcription.[243] The European Board found these distinctions important enough to confer nonobviousness, hence patentability, to the invention. In other words, it considered that the prior art did not adequately suggest the limitations, and therefore, did not render the invention obvious. The Federal Circuit reacted differently to the reading frame limitation, where it considered that "the importance of orientation and reading frame was well known in the prior art . . . ."[244] In case the reading frame had to be modified, a technique existed, which "could be used to shift the sequence of the DNA inserted into a plasmid into the proper reading frame."[245] The Federal Circuit decision does not mention the minimal size of the expressed protein required to avoid proteolytic degradation. The contrary decisions by the USPTO and the European Patent Board based on identical facts and very similar law demonstrates show how subjective the evaluation of an adequate prior art suggestion can be.

More recently, the Federal Circuit decided *In re Vaeck*,[246] another case concerning a DNA combination invention. The applicant claimed a hybrid DNA sequence (plasmid) combining a Bacillus-derived gene encoding for an insecticidal protein and a DNA promoter effective for expressing foreign genes (such as the Bacillus gene) in a cyanobacterium.[247] Both genes were separately disclosed in the prior art, as well as the expression in cyanobacterium of a foreign protein (CAT), using another promoter. The PTO Board had judged that substituting insecticidal Bacillus genes for CAT was ob-

242. *GENETECH I/Polypeptide Expression*, 4 EUR. PAT. OFF. REP. 1, 17 (1989).

243. Thus, neither the reading frame nor the size of the protein really mattered.

244. *In re* O'Farrell, 853 F.2d at 902.

245. *Id.*

246. 947 F.2d 488 (Fed. Cir. 1991).

247. *Id.* at 490. Expressing insecticidal proteins in cyanobacteria is interesting because the latter grows on top of swamps where they are consumed by mosquitoes and flies. *Id.* at 489.

vious in light of the prior art.[248] The Federal Circuit reversed, finding no suggestion of the combination in the prior art:

> The prior art simply does not disclose or suggest the expression in cyanobacteria of a chimeric gene encoding an insecticidally active protein .... More particularly, there is no suggestion in ... the primary reference cited against all claims [disclosing CAT expression in cyanobacteria], of substituting in the disclosed plasmid a structural gene encoding *Bacillus* insecticidal proteins for the CAT gene utilized for selection purposes.[249]

The court in *In re Vaeck* seems to require a fairly specific suggestion in the prior art before finding a DNA combination invention obvious. It distinguished *In re O'Farrell* from *In re Vaeck* precisely on that point, noting that in the former case the prior art explicitly suggested the combination invention. As already noted, this requirement is somewhat in contrast to the case law on combination inventions pertaining to other fields, where the suggestion need not be as specific.[250] However, this appears to be the law for biotechnology combination inventions, for the Federal Circuit recently repeated the reasoning in *In re Nunberg*,[251] a case similar to *In re O'Farrell:*

> The Board's reliance on Backman's suggestion distinguishes this case from cases lacking an *explicit* suggestion of the claimed process. For example, in *In re Vaeck*, this court reversed the obviousness rejection of claims not suggested by the prior art. Vaeck claimed expression of an insecticidal protein in cyanobacteria. The prior art taught only expression of an antibiotic enzyme. The prior art did not suggest substituting the insecticide gene for the

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248. *Id.* at 492.

249. *Id.* at 493.

250. *See, e.g.*, the concurring opinion of Chief Judge Nies in *In re* Oetiker, a mechanical case:

> I agree ... that there must be some teaching, reason, suggestion, or motivation found "in the prior art" or "in the prior art references" to make a combination to render an invention obvious within the meaning of 35 U.S.C. § 103 (1988). Similar language appears in a number of opinions and if taken literally would mean that an invention cannot be held to have been obvious unless something specific in a prior art reference would lead an inventor to combine the teaching therein with another piece of prior art.
>
> This restrictive understanding ... is clearly wrong ....
>
> ....
>
> While there must be some teaching, reason, suggestion, or motivation to combine existing elements to produce the claimed device, it is not necessary that the cited references or prior art specifically suggest making the combination."

In re Oetiker, 977 F.2d 1443, 1447-48 (Fed. Cir. 1992) (Nies, C.J., concurring).

251. *In re* Nunberg, 33 U.S.P.Q.2d (BNA) 1953 (Fed. Cir. 1994).

antibiotic gene.

> This case is very different. Backman teaches that "our method should be applicable" as Nunberg claims. Backman thus makes an *explicit* suggestion to practice the claimed process.[252]

The repeated use of the word "explicit" is significant. Although the absence of suggestion was in itself sufficient to decide for nonobviousness, the court in *In re Vaeck* also found no reasonable expectation of success in practicing the invention, without elaborating.[253]

In *Ex parte Browne,*[254] the PTO Board also examined the prior art suggestion to make a DNA combination invention in determining obviousness. In this complex case, the applicant had devised a DNA vector replicative in both bacterial and animal cells, which included SV40 early gene sequences but no late gene sequences.[255] In addition, the vector included two restriction sites, one for the insertion of an heterologous gene whose expression is wanted and the other for the insertion of SV40 late gene sequence which is able to render the vector lytic. The examiner had rejected the application as obvious from prior art references disclosing various lytic and nonlytic SV40 vectors. The PTO Board reversed, because none of these references specifically disclosed the "insertion of an SV40 functional region into a vector containing an exogenous gene to render it lytic."[256] In other words, the prior art did not suggest or motivate the inventor to make the claimed combination of prior art DNA sequences, which accordingly was nonobvious, and thus patentable. Similar to *In re Vaeck*, the PTO Board seems to require a fairly specific prior art suggestion before finding the combination invention obvious.

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252. *Id.* at 1955 (citations omitted) (emphasis added).

253. *In re* Vaeck, 947 F.2d 488, 495 (Fed. Cir. 1991). Although the Court did not directly elaborate on the lack of reasonable expectation of success, support for this finding can be found in its discussion about the lack of suggestion. Denying that the prior cloning of insecticidal proteins into bacteria would suggest doing the same in cyanobacteria, the Court stressed the differences between both types of organisms and the recent uncertainty about the biology of cyanobacteria. The same argument could have been used to demonstrate that there was no reasonable expectation of success in practicing the claimed invention. *Id.* at 494.

254. 19 U.S.P.Q.2d (BNA) 1605 (Bd. Pat. App. & Int. 1988) and 19 U.S.P.Q.2d (BNA) 1609 (Bd. Pat. App. & Int. 1990). The second decision by the PTO Board confirms and clarifies the previous one, which is nearly incomprehensible.

255. *Ex parte* Browne, 19 U.S.P.Q.2d (BNA) 1609, 1610 (Bd. Pat. App. & Int. 1990). SV stands for simian virus, commonly used as a vector in recombinant DNA technology. Early and late genes refer to genes expressed at different stages of the virus' life cycle. Late genes are required for the virus to be lytic.

256. *Id.* at 1611.

All the cases mentioned above concern DNA combination inventions. As already noted, proteins combining various functional domains could be imagined but are not yet a reality in biotechnology patent practice.[257] Nevertheless, a class of proteins, and they are already in use could be incorporated into combination inventions. These are proteins which are portions of larger prior art proteins, individualized because they represent a functional domain, an epitope, or any other region able to have an independent function or meaning. Since the sequence of such protein fragments is included in the sequence of larger prior art proteins, the only contribution of the person who develops them resides in identifying the cleavage points used to determine the new protein. Accordingly, these proteins can be viewed as the first step toward proteins combining various functional domains, because they represent the basic units of such combination inventions. Since the structure of these proteins as defined by their amino acid sequence represents only a part of their larger parents, the inquiry for structural similarity derived from traditional chemistry makes little sense.

Depending upon how one interprets the notion of structural similarity, protein fragments could be considered as similar to, or dissimilar from, their parents. They are similar because their structure is always "included" in their parent's structure, and they are dissimilar because their structure is always smaller than their parent's. The obviousness analysis for such proteins should follow the pattern used in combination inventions, focusing on whether or not the prior art provides suggestion or motivation to cleave the prior art protein at the points determining the new protein. If not, the latter should be patentable. In practice, many proteins representing fragments of larger prior art proteins and having an independent meaning or function have already been patented without problems because nothing in the prior art suggested cleaving the prior art proteins at the points defining the new ones. For example, Genetic Institute's second generation tissue plasminogen activator (FE-1X) differs from natural human t-PA in that it lacks two functional domains and one glycosylation site. Independent of an infringement suit by Genentech, holder of a patent on natural t-PA,[258] FE-1X was issued a patent without dif-

257. Shortly before this article went into publication, the Federal Circuit decided a case involving a protein combining growth hormone and an enterokinase cleavage site. *In re* Mayne, 41 U.S.P.Q.2d (BNA) 1451 (Fed. Cir. 1997). *See infra* this Part.

258. Genentech, Inc. v. Wellcome Found., Ltd., 14 U.S.P.Q.2d (BNA) 1363 (1990); 798 F.Supp. 213 (D. Del. 1992), *rev'd* 29 F.3d 1555 (Fed. Cir. 1994). Because the two deleted domains, finger (F) and epidermal growth (E), account in natural tPA for fibrin binding and

ficulty.[259] Other examples include innumerable peptides representing fragments of HIV surface proteins, patented despite the publication of the entire nucleotide sequence of HIV years before.[260] The patented peptides generally represent some domain or region important for immunogenicity or other functions.[261]

Finally, a recent Federal Circuit decision can be viewed as the first obviousness case directly discussing combination proteins.[262] The applicant had claimed a protein combining (1) the amino acid Met (an unwanted result of translation), (2) an enterokinase cleavage site (allowing Met to be eliminated), and (3) either human or bovine growth hormone (intended to be released for pharmacological action). The court first observed that growth hormones were in the prior art and that the enterokinase site in the claimed protein was structurally obvious — it differed by only one amino acid and was functionally equivalent to prior art enterokinase sites. In other words, none of the functionally significant elements of the claimed combination protein was patentable by itself. The court then found that the whole protein was prima facie obvious, citing a patent teaching the fusion of an enterokinase cleavage site to a desired protein. In other words, the court found that the prior art reference suggested the combination used to make the invention. It should be noted, however, that the court reached its conclusion even though the reference did not explicitly suggest the specific combination — here a protein including the enterokinase site and human or bovine growth hormone. This is in contrast with *In re Vaeck*, *In re Nunberg*, and *Ex parte Browne*,[263] where the courts seemed to require a fairly specific suggestion of the combination before an obviousness finding could be made. This point evidently represents a moving area of the law, which will have to be clarified in future cases.

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because FE-1X is thought to bind fibrin thanks to the glycosylation site deletion, FE-1X was found not infringing natural human t-PA under the doctrine of equivalents. Although both FE-1X and t-PA perform substantially the same function (fibrin binding), they do it in a substantially different way (t-PA through the F and E domains, FE1X through the missing glycosylation site).

259. Glenn R. Larsen, *Truncated Thrombolytic Proteins*, 1124 OFFICIAL GAZETTE OF THE U.S. PAT. AND TRADEMARK OFF. 2164 (March 26, 1991) (No. 5,002,887).

260. Lee Ratner et al., *Complete Nucleotide Sequence of the AIDS Virus, HTLV-III*, 313 NATURE 277 (1985).

261. *See, e.g.*, Lucinda A. Ivanoff & Steven R. Petteway, *Human Immunodeficiency Virus Antigen*, 1105 OFFICIAL GAZETTE OF THE U.S. PAT. AND TRADEMARK OFF. 3313 (August 29, 1989) (No. 4,861,707).

262. *In re* Mayne, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997)

263. *See supra* Part III.C (discussing these cases).

IV. CONCLUSION

This article attempts to clarify the analysis of obviousness for various recombinant inventions. It shows notably how the rationale prevailing in traditional chemistry is not valid for all categories of recombinant inventions, even though they all can be considered as "chemical compounds." Accordingly, this article distinguishes three categories of recombinant inventions: "translation" inventions, "molecular modification" inventions, and "combination" inventions. A synopsis of the obviousness analysis for these inventions, as developed in the text, is presented in Table 5.

TYPE OF INVENTION	STATUTORY DISPOSITION APPLICABLE	INVENTION IS "OBVIOUS TO A SKILLED PERSON" IF PRIOR ART PROVIDES	FACTOR USUALLY REDEEMING PATENTABILITY
Translation inventions (DNAs obtained from the corresponding protein)	35 U.S.C. § 103(a):	"basic information" underlying invention (protein sequence) + method of "translation"	no reasonable expectation of success of the method of "translation"
Molecular modification inventions (traditional chemical compounds and second generation proteins/ DNAs obtained by molecular modification)	"A patent may not be obtained if the . . . subject matter . . . would have been obvious to a person having ordinary skill in the art . . . ."	structurally similar compound(s) + motivation to make the new compound (i.e., some useful property in the prior art compound) + enabling disclosure of a method to make the new compound (prima facie obviousness)	unexpected properties in the new compound or no proper similarity, motivation, or disclosure (prima facie case rebuttal)
Combination inventions (mechanical and recombinant combination inventions)		all elements of the combination + suggestion to make the combination	no adequate suggestion to make the combination or no reasonable expectation of success

Table 5. Synopsis.

The first category — "translation" inventions — represents a new type of invention, rendered possible by the advent of the powerful "translation tool" of recombinant technology. If one turns back to

the original meaning of § 103, one realizes that if some basic information is in the prior art, translation inventions obtained by mature translation technology are obvious under current law. While obviousness of translation DNAs might not be a problem for much longer, since developers now tend to keep the underlying basic information (amino acid sequence) secret until the DNA is found, it is not the case for other biotechnology products which also potentially represent translation inventions. Monoclonal antibodies can be viewed as resulting from the translation of the molecular information contained in antigens, according to the Kohler-Milstein translation method. Ligands retrieved by combinatorial library screening on receptors could also be considered as translation inventions. Accordingly, the broader issues involved in "translation" inventions require a careful evaluation before any broad decision is made about their patentability. The Federal Circuit certainly did not make this evaluation before rendering its decision in *In re Deuel.*

In relation to the two other categories — "molecular modification" and "combination" inventions — this article has determined that the rules developed in chemical and mechanical cases are respectively applicable. Both categories concern proteins or DNAs, i.e., "chemical compounds." Accordingly, one might wonder why molecular modification inventions should be considered chemical compounds for patent law purposes while "combination" inventions should be considered mechanical devices? The reason lies in the macromolecular nature of recombinant inventions. As such, they can be contemplated either as unitary structures (whose internal logic is not understood) similar to chemical compounds; or as the combination of autonomous functional units (making sense as a whole structure) similar to mechanical devices. Due to their intermediate size (between the atomic scale of chemicals and the microscopic world of microdevices) recombinant macromolecules represent a versatile subject matter and should alternatively be assimilated to either one. Patent law will fulfill its function only by recognizing the specific nature of these inventions.

The issues discussed in this article provide an example of an existing law challenged by a major technological change. In such situations, a true understanding of both the technology and the law is required to make the right decisions. The typology of recombinant inventions offered here is a modest attempt toward this goal.