Patenting DNA—Obviousness Rejections*

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INTRODUCTION

The basic premise of this article is that all technologies should be judged by the same legal standards on the issue of obviousness,[1] and that in particular DNA should not be singled out, apart from other compounds, when determining its patentability over known DNA compounds. A DNA sequence is not merely a sequence of letters representing nucleotides linked together in a chain. DNA sequences are chemical compounds which, like other compounds, have properties and characteristics beyond acting as information transfer vehicles. Guidelines exist for determining the obviousness[2] of one claimed compound over other known compounds. Initially, the structure of the claimed compound is compared with the structure of known compounds to determine if the claimed compounds are *prima facie*[3] obvious in view of the structure of known compounds. If *prima facie* structural obviousness is found, one must consider the properties of the compounds since it is the compound as a whole with all of its properties and characteristics[4] that is to be patented and not merely

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1 The standard of obviousness under 35 USC §103 does not differ with the technology. This is well-established rule that is firmly embedded in precedent.

> The problem of "obviousness" under Section 103 in determining the patentability of new and useful chemical compounds, or, as it is sometimes called, the problem of "chemical obviousness," is not really a problem in chemistry or pharmacology or in any other related field of science such as biology, biochemistry, pharmacodynamics, ecology, or others yet to be conceived. It is a problem of *patent law*.
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> *In re Papesch*, 137 USPQ 43, 47 (CCPA 1963) (emphasis original).

The Federal Circuit has adhered to *Papesch* and has reiterated that obviousness determinations are made irrespective of the technology.

> The problem of obviousness considered by the Patent and Trademark Office, and to which we address ourselves here, arises under Section 103 of the Patent Act. It is a problem of patent law and not of chemistry. Thus, the requirement of unobviousness in the case of chemical inventions is the same as for other types of inventions.
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> *In re Johnson*, 223 USPQ 1260, 1263 (Fed. Cir. 1984) (citing *In re Papesch*, 137 USPQ 43, 47 (CCPA 1963)).

2 35 U.S.C. §103 as interpreted by *Graham v. John Deere*, 148 USPQ 459 (1966).

3 Obvious on its face. See *In re Warner et al.*, 154 USPQ 173 (CCPA 1967).

4 *In re Papesch*, 137 USPQ 43 (CCPA 1963).

its structure. Although there are numerous cases describing these guidelines,[5] such cases are virtually ignored by both practitioners and the Patent Office when determining the obviousness of genetic material.[6] Examiners and practitioners applying different standards to DNA should reconsider their position on determining the obviousness of genetic material and make such determinations based on the same criteria used to determine the obviousness of other compounds[7] until such time that legal precedents are established for applying different criteria when determining the obviousness of genetic compounds.[8] Lastly, this article provides some background information on the science of molecular genetics and makes some generalizations for the purpose of simplicity. For those in need of additional basic background information, a generalized simplistic description of the science is contained in *In re O'Farrell,* 7 USPQ 2d 1671 Fed. Cir. (1988) and publications cited therein.

5 *United States v. Adams et al.*, 148 USPQ 479 (1966) and see the cases cited in notes 14, 20, and 22 infra and note 1 supra.

6 *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 13 USPQ2d 1737 held that a prior art disclosure of an amino acid did render the gene encoding that sequence obvious. *Agmen* includes some unique facts. However, rejections issued by Examining Group 180 (now 1800) are often different from rejections issued by other Examining Groups in the Patent Office. Rejections from Group 180 regard molecular biology in an overly simplistic and predictable manner when issuing rejections under 35 U.S.C. §103 but in a complex and unpredictable manner when issuing rejections under 35 U.S.C. §112. Applicants are continually caught in a "catch-22" scenario whereby the inventions are described so well that the Examiner concludes they are obvious or they are described in a less complete manner and are rejected as not having an enabling disclosure. The 35 U.S.C. §103 rejections are overly simplistic in that they regard the claimed DNA polymers as only informational transfer vehicles while disregarding their chemical structure as well as the chemical and biochemical properties resulting from their structures. The rejections assume that the substitution of one degenerate codon for another is obvious without providing any legal or scientific basis for such an assumption. Further, the rejections assume that the number and precise combination of such substitutions are irrelevant and that therefore any number of substitutions would be obvious. In short, the rejections from Examining Group 180 argue that because any number of substitutions might be made, it would be obvious to make them.

7 As explained infra, there are no "other" compounds as DNA is a polymer and should be treated like any other polymer when determining patentability. A specific example of a PTO rejection of a synthetic DNA sequence over a naturally occurring sequence can be seen in the file history of U.S. Patent 5,096,825, issued March 17, 1992. The rejection was withdrawn after filing a Brief on Appeal, which included arguments similar to those put forth here. In another case, note the following direct quote from an Examiner's Answer in an application presently on appeal from Group 180. "Appellant's citation of chemical art case law is not deemed to be germane to the issues at hand; rather, each case is decided on its own merits. The relationship between a gene and the protein it encodes *requires a different type of obviousness determination than the structural homology of traditional chemistry.*" (emphasis added).

8 Although both Examiners and Practitioners are guilty of this duplicity the article deals with the matter via rejections applied by Examiners and not opinions offered by practitioners. Further, it is recognized that not all Examiners or practitioners make the mistake, but the problem is widespread.

Obviousness Rejections of DNA

Obviousness rejections of claims to DNA *per se*[9] generally fall in one of two categories as follows: (1) a claimed synthetic DNA sequence is rejected over a known DNA sequence which codes for the same protein[10] as the claimed DNA; or (2) the claimed DNA sequence is rejected over a known amino acid sequence which the claimed DNA encodes.[11] At first blush, the rejections appear legitimate in that the groups of three nucleotides known as codons which encode any amino acid are known as are all the possible degenerate codons.[12] If one knows which codons code for which amino acids and which degenerate codons code for the same amino acid, it might, at first, appear obvious to substitute "equivalent" codons and obtain the claimed sequence. However, making such codons substitutions

9 Claims to actual DNA sequence and not merely methods of making it or host cells containing it.

10 Not all DNA is expressed to produce a protein. However, most commercially valuable DNA sequences have their value in their ability to be used to produce protein when inserted in a host cell line. A given DNA sequence can only produce one amino acid sequence—but consider overlapping genes. However, as explained further infra, different sequences can produce the same protein.

11 For purposes of this article, the rejections (1) and (2) are considered together. Further, when the DNA sequence is known, the amino acid sequence can be readily generated. However, the reverse is not true, i.e. due to the degeneracy of the genetic code when the amino acid sequence is known, one cannot deduce the DNA sequence.

12 A sequence of three nucleotides is a codon and a codon encodes for a unique amino acid. However, there are four different nucleotides in DNA which can be combined in 64 different codon sequences. The codons are needed to produce only 20 different amino acids thus the 64 different codons provide some redundancy. When more than one codon codes for the same amino acid, the codons are referred to as degenerate codons.

is, at best, "obvious to try."[13] This article closely examines the obviousness of making such substitutions vis-á-vis the rejections (1) and (2) above.

Claiming a Synthetic DNA Sequence

For purposes of demonstration, let us assume that the claims are to DNA *per se*. Further, let us assume that the claimed DNA is 300 nucleotides (100 codons) in length and that it encodes the production of a biologically active and important protein which we will call protein XYZ which protein is expressed when the DNA is inserted into a strain W of a yeast host. Such a scenario is typical and with it the Patent Office will generally reject the claimed DNA over prior art which discloses the natural human DNA sequence which encodes XYZ. Since the claimed DNA is synthetic, we will assume it was initially produced by stepwise solid phase synthesis of single strands followed by annealing and ligation. Thereafter, multiple copies are made by cloning.

The (claimed) synthetic and (prior art) natural DNA both encode XYZ. Thus, the claimed DNA cannot be distinguished from the prior art based on the protein produced. However, such a claimed DNA sequence will (as described further herein) be distinguishable from the prior art based on (1) its structure and (2) on its various properties and characteristics beyond that of a mere information transfer vehicle.

Arguments can be made that a claimed DNA sequence is distinguishable and patentable over a known DNA sequence encoding the

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13 In the absence of some expectation of success apparent in the prior art, the references can only render the claimed invention "obvious to try," a standard which fails to meet the requirements of Section 103. Obviousness under Section 103 requires both a suggestion to perform the claimed process, *and* an expectation of success. As stated by the court in *In re Dow Chemical*, 5 USPQ2d 1529 (Fed Cir., 1988):

> The Board thus concluded that although one would not know in advance whether the Baer technique would work at all in the presence of diene rubber, or produce a moldable high-impact product, if it did succeed it would have been obvious. . . . This is not the criterion. . . .
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> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. [cites omitted] Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure.
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> The PTO presents, in essence, an "obvious to experiment" standard for obviousness. However, selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used other than the knowledge learned from the applicant's disclosure.

5 USPQ2d at 1531–32.

same protein based on structural differences alone. Since the genetic code is known, the success of such arguments in Court is questionable. However, any DNA sequence worth discussing will ultimately be inserted in a vector, the vector inserted in a host, and the host grown to commercially produce the desired protein. Therefore, when considering the patentability of a DNA sequence, one must look beyond its structure to the properties and characteristics of that structure as shown in a vector, in a host, and as actually used to make the desired protein.

In a typical situation the claimed DNA is (1) a novel chemical compound in the form of an oligonucleotide sequence synthesized to form a sequence which differs in chemical structure and biological characteristics from any other sequence which codes for XYZ; (2) designed so that it can be inserted in a vector, which vector can be expressed in a commercially useful host, e.g. a eukaryotic yeast host which we have referred to here as strain W of yeast; (3) designed so that it is effectively expressed in this host (e.g. yeast) providing a high yield of XYZ free of pyrogens and other endotoxins as compared with XYZ produced in procaryotic cells; and (4) designed so that it can produce XYZ on a commercial scale for the inclusion in pharmaceutical formulations for the treatment of humans suffering from a malfunction resulting from a deficiency of XYZ. Characteristics (2) through (4) are, of course, related in part to the structure of vectors (e.g., promoters, enhancers, termination sequence) and cellular mechanisms of the host. However, the structure of the DNA sequence may enhance all of these characteristics. Accordingly, the inventors should be afforded patent protection based on their development and contribution to the public knowledge of the DNA having all and/or any of the above-listed properties and characteristics.

Arguments Re Unobviousness

The arguments are presented below in outline form as issues I and II. Issue I is whether claims directed to a DNA sequence are *prima facie* unobvious under 35 U.S.C. §103 over prior art disclosing (1) the natural DNA sequence which codes for the production of

XYZ;[14] (2) general teachings that DNA sequences can be manipulated to obtain increased expression in a given host by choosing host preferred codons;[15] and (3) the known genetic code which teaches all possible codon equivalences.[16] Issue II is whether claims to a DNA sequence are unobvious over the art notwithstanding any showing of structural unobviousness due to the properties and characteristics of the DNA claimed.

In essence, argument I is that the claimed compounds are structurally unobvious in view of any structure disclosed in the cited art—since there is no legal precedent for holding DNA compounds to a different and generally higher standard of patentability than "other" polymers are held to. The essence of argument II is that notwithstanding any showing of *prima facie* structural obviousness of the

14 To make a valid *prima facie* case of obviousness, the rejection must include positive evidence that the bringing together of the claimed components would have been obvious to an ordinary skilled person. See *Cormetrics* and/or *In re Fine*, supra. As stated in *In re Fine* at 1599:

> Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). But it "cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination." *ACS Hosp. Sys.*, 732 F.2d at 1577, 221 USPQ at 933. And "teachings of the references can be combined *only* if there is some suggestin or incentive to do so." *Id.* Here, the prior art contains none.

15 See notes 10 and 12 supra. Although different codons encode for the same amino acid, the cellular mechanisms of each cell are designed such that they have greater compatibility with a given codon. Thus, in a given cell line, the cellular mechanisms may more efficiently produce a given protein using a preferred codon than if other less preferred codons were used. In some instances, no codons are preferred while in others, a failure to use the preferred codons will result in no expression.

16 Without a suggestion to combine the references evident in the prior art, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the court in *Panduit Corp. v. Dennison Mfgr. Co.*, 227 USPQ 337 (Fed Cir., 1985):

> In its consideration of the prior art, however, the district court erred ....in considering the claims in less than their entireties....and in considering the references in less than their entireties, i.e., in disregarding disclosures in the references that diverge from and teach away from the invention at hand....
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> •••
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> ... The result is that the claims were used as a frame, and individual naked parts of separate prior art references were employed as a mosaic to recreate a facsimile of the claimed invention.

227 USPQ at 345, citing *W.L. Gore v. Garlock Inc.*, 221 USPQ at 311, 312 (Fed Cir., 1983). The references supporting such rejections are often selected on the basis of suggesting, at best, an isolated aspect of the invention, yet none of the references together or alone suggest the combination which comprises the claimed invention. One of ordinary skill in the art, with such references before him, would find no suggestion to (1) make the claimed DNA compound, or (2) use that compound to express the desired protein in the prepared host. Indeed, without the benefit of applicant's disclosure, it would be practically impossible for one of ordinary skill to write down the claimed DNA sequence let alone synthesize it and express it in the preferred host. Clearly, such rejections are based on hindsight. Thus, no *prima facie* case of obviousness is established under Section 103.

claimed DNA compounds in view of the cited art, the claimed DNA must be considered as a whole—including all of its properties and characteristics which render the claimed invention unobvious. Quotation marks have been used around the word "other" when referring to non-DNA polymers to emphasize a point. The point being that by making such rejections, the Patent Office treats DNA polymers differently from non-DNA polymers. There is actually no such thing as "other" polymers except in the sense that the Patent Office, or at least certain Patent Office Examiners have *sua sponte* decided to treat DNA polymers differently.[17] It must be emphasized that a polymer is a polymer is a polymer whether it is DNA or polyvinylchloride. There is no such thing as other polymers[18] notwithstanding the application of different standards to DNA as opposed to non-DNA polymers which are often applied by the Patent Office. As will be understood from the following, similar arguments could be made regarding any nucleic acid sequence, e.g., mRNA, tRNA.

I. Claims to the DNA Compounds Are Not *Prima Facie* Structurally Obvious Over the Cited Art.

Typically, the prior art compounds which are most closely related structurally to the claimed compounds will be disclosed in a publication teaching the synthesis of XYZ by the expression of the natural DNA sequence (encoding for XYZ) in *E. coli.*[19] Other prior art scenarios can be readily imagined. However, provided the prior art does not disclose this claimed sequence, the particular scenario examined does not affect the validity of the arguments presented here.

Standard one letter abbreviations for the nucleotides (ATGC) can be used to compare the claimed sequence with the closest prior art sequence. The letters represent individual nucleotides or "monomer units" in the DNA polymer: A = adenine, T = thymine, G = guanine, and C = cytosine. After making the comparison, mathematical computations can be carried out to show the significance of the differences, i.e. the percent of nucleotides claimed that are different from the nucleotide of the prior art. In general, the differences

17 See note 7 supra.

18 For certain purposes such as sequence listing requirements and deposit requirements, the law has recognized DNA as different from other polymers, at least in certain instances. However, only obviousness issues are considered here.

19 This is true because research in this area generally proceeds by first finding the natural human gene and making copies of the gene in a well understood host such as a pBR322 *E. coli.* host cell.

will be of such a magnitude that if similar differences existed between any "other" claimed molecule (than a DNA molecule) and the prior art, no art rejection would be put forth.[20] For example, as much as 66.66 percent of the claimed DNA monomer units (i.e. nucleotides) could be different from the monomer units of the DNA of the prior art even though both DNA sequences encode for XYZ. If 66.66 percent of the structure of some "other" claimed compound differed from the closest prior art, it is unlikely that any obviousness rejection would be made. Further, since DNA molecules include only four bases or monomer units, on average, any two sequences (chosen completely at random, i.e., not actual) would be expected to have 25% homology. Thus art which is cited to disclose a claimed sequence which has only 25% homology with the claimed sequence is no better prior art than a sequence picked purely at random.

The case law holds that "there must be adequate support in the prior art for the change in structure in order to complete the PTO's *prima facie* case and shift the burden of going forward to the applicant."[21] In general, rejections of DNA over known DNA does not even recognize what the structural differences are let alone provide reasons for changing one structure to obtain another. The structural differences between claimed sequences and prior art sequences can be seen by showing the complete structure of the monomer units or bases known as purines and pyrimidines. In DNA, only A, T, G, and C exist. In RNA, each T will become U as is shown below.

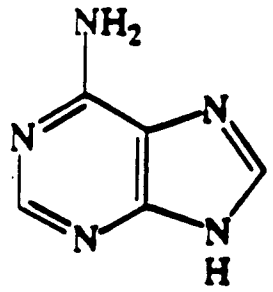
20 Chemical compounds are not rejected as obvious over known compounds which differ from the claimed compounds by important functional groups. The cases do hold that adjacent homologs, without more, are presumed to be equivalents. *In re Henze*, 85 USPQ 261 (CCPA 1950). However, the CCPA has held that the presumption of obviousness does not extend beyond adjacent members of a homologous series. See *In re Elpern*, 140 USPQ 224 (CCPA 1964) and *In re Mills*, 126 USPQ 513 (CCPA 1960). In organic chemistry, adjacent homologs often differ from each other by a $-CH_2$ group. However, even though the claimed compounds and prior art compounds differ structurally by a CH_2 group, unless their equivalency is recognized by those skilled in the art, a showing of unobviousness (e.g. a demonstration of unexpected properties) need not be made to establish patentability. See *Ex parte Thompson*, 119 USPQ 254 (POBA 1954) and *In re Shetty*, 195 USPQ 753 (CCPA 1977). The mere fact that a claimed compound has an empirical formula which differs from a prior art compound by one or more CH_2 groups does not establish these compounds as members of the same homologous series. *Ex parte Burtner*, 121 USPQ 345 (POBA 1951).

21 *In re Grabiak*, 226 USPQ 870 at 872 (Fed. Cir. 1985).

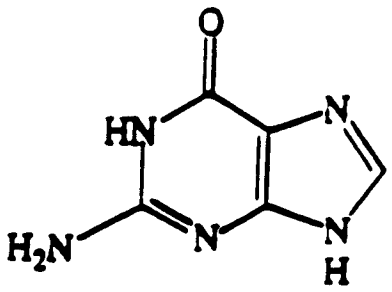
DNA template	transcription	mRNA	translation	protein
GAT	→	CUA	→	leucine
AAC	→	UUG	→	leucine

The actual structure of the bases followed by the structure of DNA templates is shown below.

purines

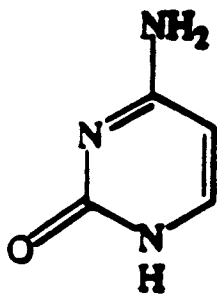


A=adenine
6-aminopurine

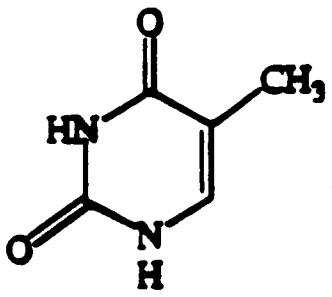


G=guanine
2-amino-6-oxypurine

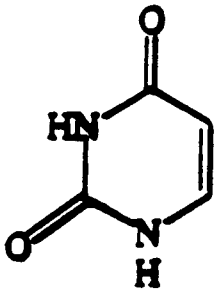
pyrimidines



C=cytosine
2-oxy-4-amino
pyrimidine

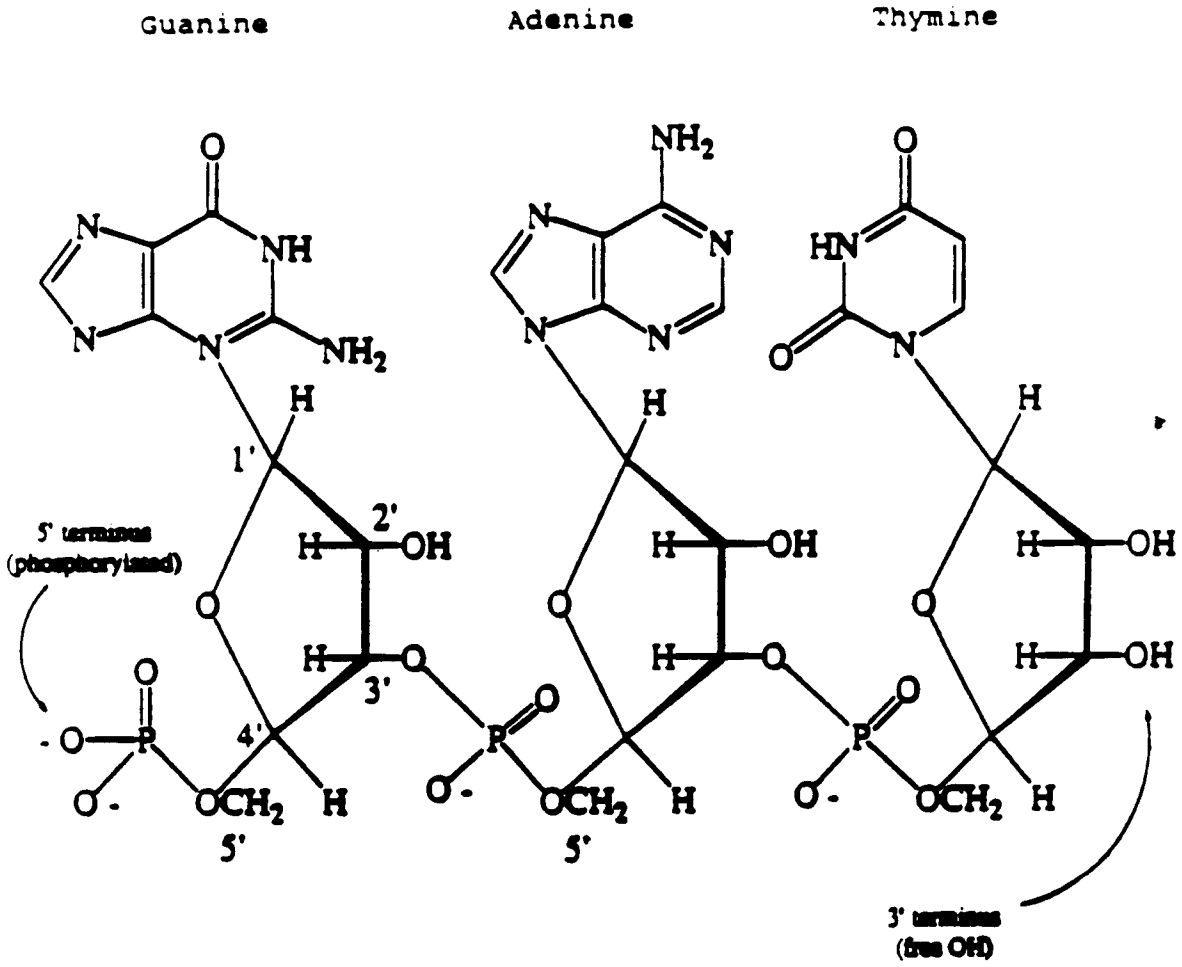


T=thymine
5-methyl-2,4-
dioxypyrimidine



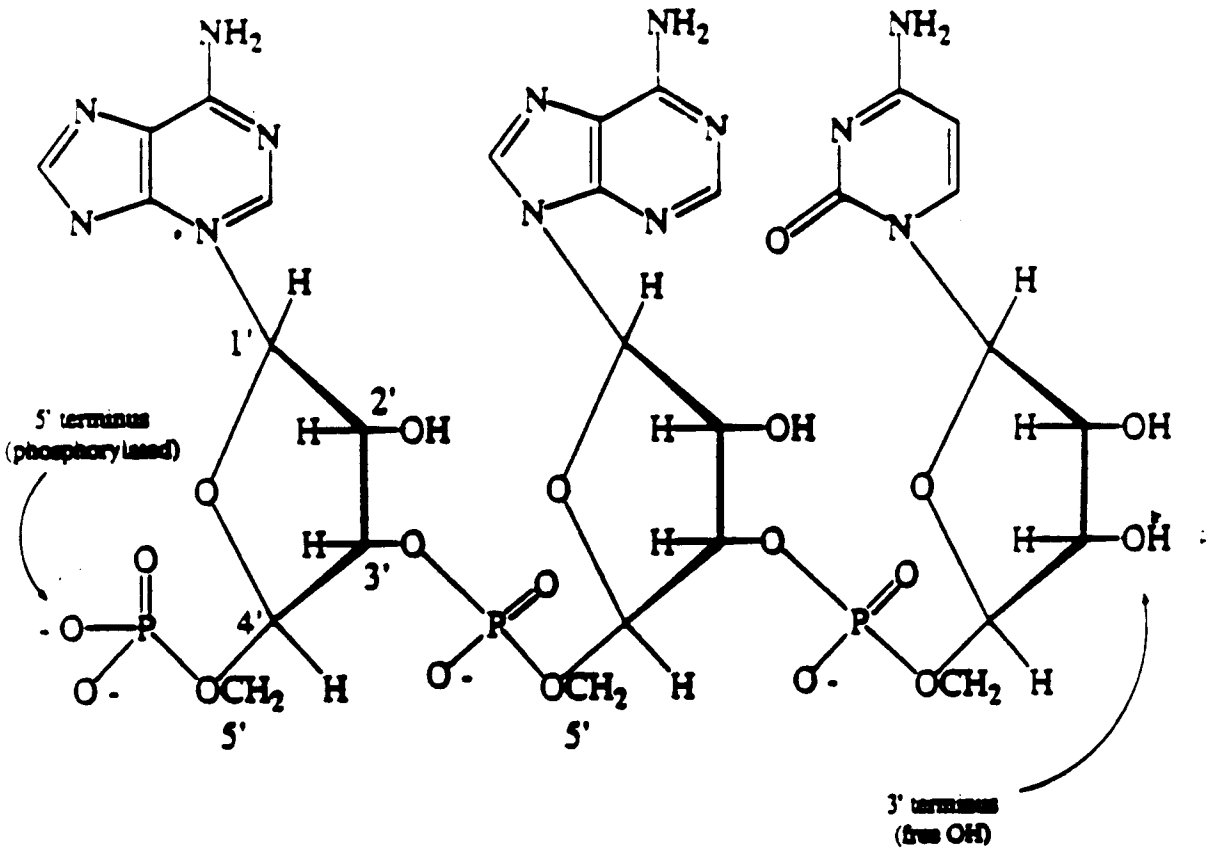
U=uracil
2,4-dioxypyrimidine

When the three bases GAT form a codon in a DNA polymer, the codon structure looks like CODON Q shown below. The CODON Q undergoes transcription to become messenger RNA of CUA which undergoes translation to become leucine.



The above CODON Q codes for the amino acid leucine. However, due to the degeneracy of the genetic code, the following CODON R which includes bases AAC is transcribed to mRNA of UUG which is translated to the protein leucine.

Adenine Adenine Cytosine



A comparison of the above structural formulae for CODON Q with bases GAT and CODON R with bases AAC shows possible structural differences between a single codon of a claimed synthetic DNA compound and a single codon of a prior art naturally occurring DNA compound. In a sequence containing 300 bases or 100 codons it is not unusual to have a large percentage of codons which are different from the natural codons. The number of differences can be determined by a sequence comparison and computation. Based on the above structural differences (and the sequence comparison and

computations) current cases[22] would not hold that the rejection presents a *prima facie* case of structural obviousness.[23]

To reject a claimed DNA sequence as obvious over a known DNA sequence, the rejection must establish that the structure of the claimed sequence is obvious in view of a DNA structure shown in the art.[24] To do this, the rejections assume the interchangeability of certain bases. More specifically, the rejections recognize that the genetic code has established certain codons encode a particular amino acid and the degeneracy of the code recognizes that other degenerate codons encode the same amino acid. Thus, the rejections assume the interchangeability of codons which encode for the same amino acid. Such rejections are based on "obvious to try" standards.

Knowledge of the genetic code results in the assumptions which form the basis of such rejections. However, the rejections are contrary to the current case law interpreting the statutes with respect to chemical inventions. The presumption of structural obviousness of one compound over another does not extend beyond adjacent members of a homologous series.[25] When a claimed compound is not a homolog of a prior art compound, the burden is on the Patent Office to show that it would have been obvious to those skilled in the art (based on the art of record) to derive the claimed compounds from the prior art compounds.[26] Rejections based on the interchangeability of degenerate codons make no showing of structural obviousness and are therefore unfounded.

Prior art can be cited to emphasize that the genetic code is known, i.e. that the correspondence between three nucleotide codons and the amino acids they code for is known. It is well known that

22 Id. and see also *In re May*, 197 USPQ 601 (CCPA 1978) (stereoisomers); *In re Wilder*, USPQ 426, 429 (CCPA 1977) (adjacent homologes and structural isomers); and *In re Hoch*, 166 USPQ 406 (CCPA 1970) (acid and ethyl ester).

23 When dealing with chemical cases not involving DNA, the Board of Appeals would not extend the doctrine of homology to embrance compounds having an alkylene group between a ring and ester function of a prior art compound. See *Ex parte Biel*, 124 USPQ 109 (POBA 1958); *Ex parte Goonewardene et al.*, 160 USPQ 287 (POBA 1968); and *Ex parte Nathan and Hogg*, 121 USPQ 349 (POBA 1956). Thus, the Patent Office, while dealing with chemical held that by inserting a CH_2 group between a -CO and -COOH group of -CO-COOH, a patentable difference existed even without a showing of unexpected results. See *Ex parte Burtner*, 89 USPQ 547 (POBA 1950). Note that each of the bases ATG and C differ from each other by more than a $-CH_2$ group.

24 *Comr. Pats v. Deutsche Gold-und-Silber*, 157 USPQ 549 (CADC 1968) and *In re Taborsky*, 183 USPQ 50 (CCPA 1974).

25 See *In re Elpern*, 140 USPQ 224 (CCPA 1964) and *In re Mills*, 126 USPQ 513 (CCPA 1960).

26 See *Ex parte Blumenthal*, 114 USPQ 513 (POBA 1956).

there are degeneracies in that code—i.e. that a given amino acid can be coded for by more than one codon sequence of three nucleotides.[27] However, knowledge of the genetic code and its degeneracies establishes only general information as regards DNA, such as the general information the periodic table establishes as regards "other" polymers. Both establish basic generalized information about *possible* equivalences, but neither can provide enough information to predict a specific result when so-called equivalent substitutions are made and the resulting new molecule is tested in a given system—especially a system as complex as a cell.

The greater the number of substitutions, (1) the more likely others would not contemplate such; and (2) the more difficult it becomes to predict the characteristics of the resulting compounds. Thus, the unobviousness of the structure and its properties increases as the number of substitutions, one base for another, increases. This is equally true for DNA molecules and "other" polymers. There is no legal basis for treating DNA polymers differently from "other" polymers.[28] Further, the molecules cannot be separated on a scientific basis as "living" and "non-living" as there is no point (presently known) at which the breath of life is infused in ascending from carbon atom o nucleotides to DNA to viruses to cells to humans.

One means of establishing a *prima facie* case of structural obviousness is to cite art which discloses the next higher or next lower homolog to the compound claimed. The CCPA has defined a homologous series as a family of chemically related compounds, the composition of which varies from member to member by CH_2 (one atom of carbon and two atoms of hydrogen).[29] Examples of such homologues are methane, ethane, propane, etc., which are members of an alkane series. However, synthetic DNA compounds are not homologues of the natural DNA. There does not appear to be any term which would describe the relationship between a claimed synthetic DNA and naturally occurring DNA. More importantly, there is no legal precedent which would establish that the synthetic DNA is obvious in view of the natural DNA.

27 See for example *Modern Concepts in Biochemistry*, 5th ed. by R.C. Bohinski Allyn and Bacon, Inc. at page 374.

28 See note 1 supra.

29 *In re Coes, Jr.* (CCPA 1949) 173 F.2d 1012, 81 USPQ 369. The Court of Appeals for the District of Columbia applied a broader definition and defined a homolog (or homologue) as a member of a series of compounds in which each member differs from the next member by a constant number of atoms. *Comr. Pats. v. Deutsche Gold-und-Silber, etc.* (CADC 1968) 397 F.2d 656, 157 USPQ 549.

The Patent Office has never legally established the obviousness of any given substitution of one base for another or one codon for another. Further, they have not established the obviousness of making large numbers of such substitutions. Although any given single base or codon substitution by itself might be considered obvious,[30] in the absence of a specific reason to make a given substitution, the obviousness of making substitutions becomes less and less clear as the number of substitutions increases. This is true whether the substitution is made using the periodic table [e.g. one alkali metal for another (Na for Li)] or using the genetic code to substitute one codon for another. The mathematical improbability of making larger and larger numbers of substitutions points in the direction of unobviousness. In general, the number of substitutions needed to obtain a given DNA molecule based on the natural DNA would be highly improbable.

II. The Properties and Characteristics of the DNA Compounds Render Them Unobvious Notwithstanding Any Showing of *Prima Facie* Structural Obviousness.

The above arguments endeavor to establish unobviousness when the prior art does not suggest the structure of a claimed DNA sequence due to multiple substitutions of codons. However, notwithstanding the obviousness of any number of such substitutions, a typical synthetic DNA sequence will have properties and characteristics which render it unobvious over the cited art within the meaning of 35 U.S.C. §103. The law is well settled that questions of chemical obviousness cannot be decided on the basis of structure alone.[31] The crucial question is what effect such obviousness of structure has upon the obviousness of the subject matter as a whole—including all of its properties and characteristics.

30 The above arguments and cites related to obviousness have been focused on homologs. However, there are cases relating to other structural relationships between compounds such as "isomers", e.g. compounds having the same radicals or functional groups at different positions on a nucleus are "positional isomers". One positional isomer is not necessarily obvious in view of another. The test is whether the claimed compounds are so closely related that the teachings of one suggests the other. See *Ex parte Simons*, 103 USPQ 221 (POBA 1952) and *Ex parte Brouard*, 201 USPQ 538 (POBA 1976). The substitution of one degenerate codon for another, in a long sequence, might well be considered obvious absent a showing of improved unexpected results.

31 See *In re Papesch* (CCPA 1963) 315 F.2d 381, 137 USPQ 43. Structural obviousness alone is not a bar under 35 U.S.C. §103 to the grant of a patent on a chemical compound, see *Comr. Pats v. Deutsche Gold-und-Silber, etc.* (CADC 1968) 397 F.2d 656, 157 USPQ 549).

When DNA molecules are viewed merely as information transfer vehicles, other important properties of the molecules are overlooked. When degenerate codons are substituted, the resulting molecules may have different and unpredictable properties relating to polymerase affinity, transcriptional fidelity, endonuclease digestion, etc., and such properties can vary greatly depending upon the host system within which the molecule is transcribed. The physiological features of the intracellular environment are complex to the extent that effects of that environment on different degenerate codons cannot be predicted. The inability to predict properties and characteristics points towards unobviousness in that the law is well settled that all of the properties and characteristics of the claimed invention must be considered as a whole when considering the issue of obviousness.

Landmark cases in this area clearly establish that "From the standpoint of patent law, a compound and all of its properties are inseparable; they are one in the same thing."[32] Any graphic formula or DNA sequence is nothing more than symbols which represent chemical nomenclature and formulas. The study of such formulas, sequences or concepts such as homology, isomerism and degeneracy provide terminology by which compounds and sequences can be identified, classified and compared. However, a chemical formula or a DNA sequence is not a compound and while it may serve in a claim to identify what is being patented, as the metes and bounds of the deed identify a plot of land, the thing that is patented is not the formula, but the compound identified by it. The patentability of the thing does not depend on the similarity of its formula to the formula of another compound, but of the similarity of the former compound to the latter. There is no basis in law for ignoring any property in making such a comparison whether the comparison is the comparison of chemical compounds or the comparison of DNA sequences. An assumed similarity based on a comparison of formulae alone must give way to evidence that the assumption is erroneous.[33]

It is well settled that a *prima facie* case of obviousness can be rebutted by showing improved, unexpected results.[34] One can often

32 See *In re Papesch* at page 51.

33 Id.

34 Regardless of how strong a case of *prima facie* obviousness made by the Patent Office, it must be weighed against factors to the contrary brought out by the applicant. See *In re Lewis*, 170 USPQ 84 (CCPA 1971) and *In re Carleton*, 202 USPQ 165 (CCPA 1979). *Prima facie* obviousness is a legal conclusion, not a fact. Therefore, facts rebutting such a conclusion must be considered along with the facts on which the conclusion was reached, not against the conclusion.

demonstrate such results by showing that the claimed DNA can be used for more efficiently expressing the desired XYZ protein in a preferred strain W of the yeast host. The prior art often provides no expectation or suggestion that the desired protein can be so expressed—or said differently, the prior art often provides no suggestion of a DNA sequence (such as that claimed) which has properties and characteristics which would allow it to be expressed in any given preferred host. It is often unobvious at the time of the invention that the claimed sequences could be expressed at all in the preferred host and clearly unobvious that they would be highly expressed.[35] Thus, notwithstanding the validity of any arguments on the *prima facie* structural obviousness of the claimed DNA, the properties of the sequence often render the invention unobvious.

One of the critically important characteristics of the claimed compounds is often their ability to be used (essentially as chemical intermediates) in a host to produce the desired protein. Conspicuously absent from any of the cited art is often a suggestion that the desired protein should be (or could be) expressed in the preferred host. It is well known that certain proteins are toxic to particular hosts and cannot be easily expressed. Some hosts degrade recombinant proteins rapidly, such that little or no product is recoverable. Some hosts (and probably most hosts) possess endogenous endonucleases which may cleave within the sequence of a synthetic gene, although the systems are designed to prevent cleavage of the natural DNA sequence. Thus, the art often provides no expectation of success that the claimed invention would work, i.e. that the combination of sequence and host would express the XYZ protein.[36] Just as a chemical compound and

35 This is true because the art can not provide useful teachings with respect to a novel DNA sequence on matters such as polymerase affinity, transcriptional fidelity and endonuclease digestion especially when the DNA is in a new host cell.

36 In deciding the question of obviousness under 35 U.S.C. §103, it is not realistic to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts of the reference necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. The mere existence in the prior art of individual features of a claimed invention does not, without more, render the invention unpatentable under current interpretations of 35 U.S.C. §103. (See *Cormetrics Medical Systems v. Berkeley Bio-Engineering*, 193 USPQ 467, 475 N.D. Calif., 1977). The inventors were the first to show the synthetic synthesis of and expression from the claimed DNA sequence. The cited art is often totally void of any suggestion of the claimed sequence, let alone show the sequence in the preferred host in a compatible vector and/or its properties, such as its usefulness in making the desired protein while in the preferred host. Any claimed combination of the DNA sequence in a vector-compatible with the specific preferred host is unobvious due to the different structure and properties of that vector as demonstrated in the preferred host.

its properties are inseparable, a DNA molecule and *all* of its properties (not merely its information transfer characteristics) are inseparable and can be relied on to establish patentable unobviousness.[37]

There are additional reasons why it is not generally possible to predict that a particular DNA can be transcribed and translated in a particular host in order to produce the desired protein. The DNA or mRNA transcript might be incompatible with some essential functions of the particular host; e.g. the mRNA might bind to a critical genetic regulator element. If the claimed DNA sequence had not previously been included within the host being used, there would be no basis for predicting the compatibility of the sequence or its operability within the particular host.

At the time of the invention, the XYZ protein would never have been expressed in a particular host, e.g. a strain W of yeast. There would be no basis for predicting that the desired XYZ protein would not be toxic to the W yeast host. Toxicity of foreign proteins to recombinant expression hosts cannot be reliably predicted. A valid rejection would require citing art (showing the DNA and the host) showing that one would expect a reasonable likelihood of success or the rejection would not meet the *prima facie* showing required by 35 U.S.C. §103.[38] In general, the rejection will not include and the Examiner will not be able to cite art which discloses, in a reliable manner, the predictability of toxicity of foreign proteins to recombinant expression hosts because such art will not exist.

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37 See *In re Lamboy*, 133 USPQ 271 (CCPA 1962).

38 It would be virtually impossible to obtain patent protection on any invention if, after making a disclosure of the invention to the Patent Office, the Examiner searched through the prior art in order to piece together portions of earlier patents utilizing only the hindsight provided by the teachings disclosed within the application. (See *Webster Loom Co. v. Higgins*, 105 U.S. 580, 591, L.Ed. 1177 and *Bragg-Kliesrath Corp. v. Farrell*, 36 F.2d 845, 850 (2d Cir. 1929)). The cited art often does not even teach the individual components of the claimed combination. Such rejections often do nothing more than cite individual references for their disclosure of individual components and disregard what each reference might fairly teach one skilled in the art. If the claims are to be rejected over a combination of references, there must be some suggestion or teaching in the references that leads to their combination (*In re Regel*, 188 USPQ 136, 139 (CCPA 1975)).

Many inventions are prepared from the combination of elements old in the art; however, if the combination is nonobvious, the invention is still patentable. It is the *combination* that must be taught in the art, not merely the individual elements. Similarly, if the disclosure of a cited reference must be modified in some way in order to achieve the claimed invention, the reference must disclose or suggest the modification in order to render the claimed invention obvious (*In re Gordon*, 221 USPQ 1125, 1127 (CAFC 1984)). Rejections often do not explain why the art would be obvious to combine and/or how it should be modified to obtain the claimed invention. Such rejections should be reversed.

The case law holds that a compound is not obvious if there is no known or obvious way to prepare it.[39] The difficulty with respect to synthesizing a particular DNA polymer may further emphasize the unobviousness of such a polymer. The strength of this argument will vary from molecule to molecule. However, as synthesis techniques improve the validity of such an argument continues to weaken.

Codon selection is governed by parameters which are rarely considered by the Patent Office. For example, it might create translation problems if the mRNA created from the DNA template forms hairpins, stems, loops or other structures. Such structures not present in the natural mRNA, could prevent the translation of the mRNA and eventually the formation of the desired protein. In that all of these parameters need to be considered, it is clear that the design of a particular claimed DNA polymer is far from an arbitrary design and that the design requires great skill so that the resulting polymer satisfies all of the complex and interdependent design criteria.

CONCLUSION

There are legitimate reasons for treating the patentability of genetic material differently from the patentability of other chemical compound. Deposit requirements and sequence listing requirements are good examples of such. However, on the issue of obviousness, all compounds, including DNA, should be treated by the application of the same legal standards.

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39 *In re Hoeksema*, 158 USPQ 596 (CCPA 1968), *In re Riden et al.*, 138 USPQ 112 (CCPA 1963) and *Ex parte Argoudelis*, 157 USPQ 437 (POBA 1967).