

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte BRIAN D. ALMOND,
MONIKA G. WOOD, and KEITH V. WOOD

Appeal 2008-2164¹
Application 10/314,827
Technology Center 1600

Decided: July 22, 2008

Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims 1-46 and 48-50 (Reply Br. 3). Pending claims 51-57 and 59-64 have been withdrawn from consideration (App. Br. 4; Reply Br. 3). During the Oral Hearing

¹ Oral Hearing held June 17, 2008.

Appellants' representative stated that Appellants will cancel claims 47, 58, and 65 (Oral Hearing Transcript 4). Accordingly, we have not included these claims in our deliberations. In the event of further prosecution, we encourage the Examiner and Appellants to work together to insure that these claims are cancelled from the record. We have jurisdiction under 35 U.S.C. § 6(b).

INTRODUCTION

Claims 1, 11, and 14 are illustrative:

1. A synthetic nucleic acid molecule comprising nucleotides of a coding region for a fluorescent polypeptide having a codon composition differing at more than 25% of the codons from a parent nucleic acid sequence encoding a fluorescent polypeptide, wherein the synthetic nucleic acid molecule has at least 3-fold fewer transcription regulatory sequences relative to the number of such sequences in the parent nucleic acid sequence.

11. The synthetic nucleic acid molecule of claim 1, wherein the synthetic nucleic acid molecule encodes a green fluorescent polypeptide that was derived from a nucleic acid molecule that was originally isolated from *Montastraea cavernosa*.

14. The synthetic nucleic acid molecule of claim [1], wherein the parent nucleic acid sequence encodes a green fluorescent polypeptide isolated from *Montastraea cavernosa*.

The Examiner relies on the following prior art references to show unpatentability:

Sherf	US 5,670,356	Sep. 23, 1997
Donnelly	WO 97/47358	Dec. 18, 1997

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Zolotukhin	US 5,874,304	Feb. 23, 1999
Cornelissen	US 5,952,547	Sep. 14, 1999
Hey	US 6,169,232 B1	Jan. 2, 2001

Catherine A. Kappel et al., *Regulating gene expression in transgenic animals*, 3 CURRENT OPINION IN BIOTECHNOLOGY 548-553 (1992).

Linda J. Mullins et al., *Transgenesis in Nonmurine Species*, 22(4) HYPERTENSION 630-633 (1993).

Peter Wigley et al., *Site-specific Transgene Insertion: an Approach*, 6 REPROD. FERTIL. DEV., 585-588 (1994).

John J. Mullins et al., *Perspectives Series: Molecular Medicine in Genetically Engineered Animals*, 97(7) J. CLIN. INVEST. 1557-1560 (1996).

Weiqing Pan et al., *Vaccine candidates MSP-1 from Plasmodium falciparum: a redesigned 4917 bp polynucleotide enables synthesis and isolation of full-length protein from Escherichia coli and mammalian cells*, 27(4) NUCLEIC ACIDS RESEARCH 1094-1103 (1999).

GenBank Accession No. AF406766, Sep. 2001.

GenBank Accession No. AY037768, May 2002.

GenBank Accession No. AY037769, Apr. 2002.

The rejections as presented by the Examiner are as follows:

1. Claims 1-11, 13-46, and 48 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

2. Claims 1-11, 13, 14, 16-35, 37-46, and 48-50² stand rejected under the written description provision of 35 U.S.C. § 112, first paragraph.
3. Claims 1-11, 13, 14, 16-32, 34, 37-46, and 48-50 stand rejected under the enablement provision of 35 U.S.C. § 112, first paragraph.
4. Claims 1-10, 13, 16-35, 37-46, and 48 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Zolotukhin, Sherf, Donnelly, Pan, Cornelissen, and Hey.
5. Claims 11, 14, 49, and 50 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Zolotukhin, Sherf, Donnelly, Pan, Cornelissen, Hey and any one of GenBank Accession No. AF406766, AY037768, or AY037769.

We affirm rejections 2, 4 and 5 and reverse rejections 1 and 3.

DISCUSSION

Definiteness:

1. Claims 1-46, and 48 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

The Examiner finds that the claims are indefinite in the recitation of the terms “‘transcription regulatory sequences’, ‘transcription factor binding sequences’ ‘intron splice sites’, ‘poly(A) addition sites’ and ‘promoter

² While the Examiner did not include claims 49 and 50 in the statement of the rejection, the Examiner clearly addressed these claims at pages 9-10 of the Answer. Accordingly, we find that the omission of claims 49 and 50 in the statement of this rejection to be a typographical error. Further, we recognize Appellants’ assertion that the Examiner did not enter an amendment to claim 49 which was filed in an attempt to address the written description issue relative to this claim (Reply Br. 11). We note, however, that the entry or non-entry of an amendment is a petitionable, not an appealable, issue. Accordingly, we will not address this issue further.

sequences' as . . . one could never obtain a count of the number of such sequence[s] in any nucleic acid” (Ans. 7). According to the Examiner “[w]hile there are clearly art defined specific sequences within each of these categories, each of them is an open-ended group of sequences which includes many unknown members” (*id.*). In this regard, the Examiner finds that

[w]ithout knowing which of these are included in the scope of the term, a quantitative value for how many are present in any nucleic acid cannot be obtained and the value obtained for any specific nucleic acid by different individuals would be different if they used different definitions of what sequences are encompassed in each of these terms.

(Ans. 8.)

In response Appellants assert “one of skill in the art would understand the metes and bounds of ‘transcription regulatory sequences,’ ‘transcription factor binding sequences,’ ‘intron splice sites,’ ‘poly(A) addition sites’, and ‘promoter sequences’ in the claims” (App. Br. 13). According to Appellants “Breadth is not indefiniteness” (Reply Br. 9). We agree. “[B]readth is not to be equated with indefiniteness.” *In re Miller*, 441 F.2d 689, 693 (CCPA 1971).

Accordingly, we reverse the rejection of claims 1-46 and 48 under 35 U.S.C. § 112, second paragraph as being indefinite.

Written Description:

2. Claims 1-11, 13, 14, 16-35, 37-46, and 48-50 stand rejected under the written description provision of 35 U.S.C. § 112, first paragraph.

Appellants provide separate arguments for claims 1, 11, and 14. Accordingly, we limit our discussion to claims 1, 11, and 14. 37 C.F.R. § 41.37(c)(1)(vii).

The Examiner finds that while Appellants' Specification discloses the structure of a "few representative species" of the claimed nucleic acids, "the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a fluorescent polypeptide" (Ans. 8-9). According to the Examiner

[t]he only identifying characteristics discussed relate to the differences between the synthetic nucleic acid and the parent nucleic acid (i.e., the synthetic nucleic acid[] differs from a parent nucleic acid at more than 25% of the codons of the parent nucleic acid, . . . [and] has at least 3-fold fewer transcription regulatory sequences than the parent.

(Ans. 9.)

Claim 1:

Claim 1 is drawn to a synthetic nucleic acid molecule. The claimed synthetic nucleic acid molecule comprises:

- a) nucleotides of a coding region for a fluorescent polypeptide having a codon composition differing at more than 25% of the codons from a parent nucleic acid sequence encoding a fluorescent polypeptide, and
- b) at least 3-fold fewer transcription regulatory sequences relative to the number of such sequences in the parent nucleic acid sequence.

The Examiner interprets claim 1 as requiring the synthetic nucleic acid to encode a fluorescent polypeptide (Ans. 8). During the Oral Hearing, Appellants' representative agreed with this interpretation that the synthetic nucleic acid molecule does indeed encode a fluorescent polypeptide (Oral

Hearing Transcript 5 and 9-10). In addition, we interpret the phrase “differing at more than 25% of the codons from a parent nucleic acid sequence” to read on a nucleic acid whose codons differ by at least 99% from those of a parent nucleic acid sequence.

Appellants assert that “prior to the filing date of the present application, nucleotide sequences encoding, and amino acid sequences for, fluorescent polypeptides were known” (App. Br. 15). While this is true, it does not address the Examiner’s concerns relating to whether Appellants’ Specification has written descriptive support for the genus of synthetic nucleic acid molecules within the scope of claim 1. As the Examiner points out “these known fluorescent proteins are clearly not representative of the structure of any fluorescent protein as is currently claimed”, e.g., a nucleic acid whose codons differ by at least 99% from those of a parent nucleic acid sequence (Ans. 25-26). We agree. Accordingly, we are not persuaded by Appellants’ assertion.

We are also not persuaded by Appellants’ assertion that their Specification provides “at least six synthetic nucleic acid sequences with a reduced number of TRS [transcriptional regulatory sequence] relative to a corresponding parent nucleic acid sequence as a result of codon replacement with codons preferred in a mammalian cell” (App. Br. 16).

As the Examiner points out, claim 1 is not “limited to synthetic nucleic acids which encode the same amino acid sequence as the parent nucleic acid” (Ans. 27). Further, as discussed above claim 1 reads on a nucleic acid whose codons differ by at least 99% from those of a parent nucleic acid sequence and thus could differ in amino acid sequence at more than 99% of the amino acid positions of the parent sequence. Accordingly,

the question is which of the synthetic nucleic acids encompassed within the genus of claim 1 that differ by more than 25%, or by at least 99%, of the codons from a parent nucleic acid sequence and having at least 3-fold fewer transcription regulatory sequences relative to the number of such sequences in the parent nucleic acid sequence will encode a functional fluorescent polypeptide?

A chemical genus can be described by structural description of a representative number of the species within the genus or by describing “structural features common to the members of the genus, which features constitute a substantial portion of the genus.” *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997). The structural description does not necessarily require disclosure of the compound’s complete chemical structure:

the written description requirement can be met by ‘show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics.’

Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964, (Fed. Cir. 2002) (emphasis and alteration original).

Appellants’ Specification does not disclose *which* of the many synthetic nucleic acid molecules encompassed by claim 1 will encode a functional fluorescent polypeptide. While Appellants disclose six species within the claimed genus, Appellants have not demonstrated that these six species are representative of the entire genus of compounds or that they share “structural features common to the members of the genus, which

features constitute a substantial portion of the genus.” *Cf. Eli Lilly*, 119 F.3d at 1569.

Further, while claim 1 requires the modifications to be made relative to a parent molecule there is no requirement in the claim that any structural feature of the parent molecule be retained other than its functional activity. In this regard, it cannot be overemphasized that claim 1 reads on a nucleic acid molecule that differs from a parent molecule by at least 99% of its codons, with no requirement that the amino acid sequence of the parent be retained.

Simply stated Appellants have failed to establish a correlation between the structure and function of the claimed polypeptides that is common to the members of the genus. Appellants’ citation of “Matz et al., Nature Biotech., 17:969 (1999)” (Reply Br. 11), to provide evidence of the “structural similarities of exemplary fluorescent proteins by an amino acid sequence alignment” is unavailing because, as discussed above, there is no requirement in the claim that any structural similarity (e.g., codon or amino acid from the parent) be retained.

For the foregoing reasons, we affirm the rejection of claim 1 under the written description provision of 35 U.S.C. § 112, first paragraph. As they were not separately argued, claims 2-10, 13, 16-35, 37-46, and 48-50 will fall together with claim 1. 37 C.F.R. § 41.37(c)(1)(vii).

Claim 11:

Claim 11 depends from and further limits claim 1 to require that the synthetic nucleic acid molecule encodes a green fluorescent polypeptide that

was derived from a nucleic acid molecule that was originally isolated from *Montastraea cavernosa*.

According to Appellants

claim 11 recites structure (i.e., a synthetic nucleic acid molecule having a codon composition differing at more than 25% of the codons and having at least 3-fold fewer TRS relative to the number of such sequences in a parent nucleic acid sequence), function (i.e., the synthetic nucleic acid molecule encodes a green fluorescent polypeptide and the parent nucleic acid sequence encodes a fluorescent protein), and the relationship between the synthetic nucleic acid molecule and the parent nucleic acid sequence.

(App. Br. 16-17; *see also* Reply Br. 11.)

While claim 11 limits the scope of the fluorescent polypeptide to a green fluorescent polypeptide, “derived” from a particular source, it suffers from the same deficiencies as claim 1. In addition, we note that according to claim 11 the green fluorescent polypeptide is “derived from a nucleic acid molecule that was originally isolated from *Montastraea cavernosa*” (Claim 11). Accordingly, the starting material for this claimed nucleic acid is something other than (*e.g.*, it structurally differs from) the green fluorescent polypeptide of *Montastraea cavernosa*. Accordingly, we are not persuaded by Appellants’ assertion that they have provided adequate written descriptive support for claim 11.

Accordingly, we affirm the rejection of claim 11 under the written description provision of 35 U.S.C. § 112, first paragraph.

Claim 14:

Claim 14 depends ultimately from and further limits claim 1 to require that the parent nucleic acid sequence encodes a green fluorescent polypeptide isolated from *Montastraea cavernosa*.

Appellants make the same structure/function argument as was presented for claim 11 (App. Br. 17; *see also* Reply Br. 11). While, in contrast to claim 11, the parent nucleic acid sequence of claim 14 is one that encodes a green fluorescent polypeptide isolated from *Montastraea cavernosa*; this claim suffers from the same written descriptive support deficiencies as claim 1. Accordingly, we are not persuaded by Appellants' assertions to the contrary.

Therefore, we affirm the rejection of claim 14 under the written description provision of 35 U.S.C. § 112, first paragraph.

Enablement:

3. Claims 1-11, 13, 14, 16-32, 34, 37-46, and 48-50 stand rejected under the enablement provision of 35 U.S.C. § 112, first paragraph.

The Examiner asserts that Appellants' Specification does not reasonably provide enablement for any variant nucleic acid molecules encoding any fluorescent polypeptide or a fluorescent polypeptide having at least 85% identity to a wild type polypeptide and having more than 25% of the codons altered and having at least 3 fewer transcription regulatory sequences than the parent nucleic acid or to any nucleic acid which will hybridize to SEQ ID NO: 1 under high stringency conditions.

(Ans. 10-11.)

According to the Examiner

[s]ince the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved . . . and detailed knowledge of the ways in which the proteins' structure relates to its function.

(Ans. 11-12.)

In addition, the Examiner finds that

it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. . . . [O]ne skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

(Ans. 12.)

In response, Appellants assert that “[o]ne skilled in the art, having read the specification, would know how to make and use one or more synthetic nucleic acid molecules that encode a fluorescent polypeptide that is not identical in amino acid sequence to a fluorescent polypeptide encoded by a particular parent nucleic acid molecule” (App. Br. 18). In this regard, we note that Appellants outline the steps of required to prepare the claimed synthetic nucleic acid molecule (Spec. 45-46). “It is undisputed that by 1988 those skilled in the art knew several techniques for altering genetic

sequences, including deletion and point mutations.” *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052, 1070 (Fed. Cir. 2005). Further, the Zolotukhin, Sherf, Donnelly, Pan, Cornelissen, and Hey references, relied on by the Examiner and discussed below, appear to run counter to the Examiner’s assertion that undue experimentation would be required on this record. “Enablement is not precluded by the necessity for some experimentation such as routine screening.” *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988).

In sum, the Examiner failed to provide an evidentiary basis to support a conclusion that it would require undue experimentation to make and screen any or all mutations within the scope of the claimed invention. The mere fact that additional experimentation is necessary does not mandate a conclusion that such experimentation would have been considered to be “undue” in this art.

The Examiner has also failed to provide an evidentiary basis to support a conclusion that once made; a person of ordinary skill in the art would not be able to use a claimed nucleic acid that falls within the scope of Appellants’ claimed invention. Here, as in *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), we find no evidence to support the Examiner’s assertion that undue experimentation will be required by those skilled in the art to practice Appellants’ claimed invention.

For the foregoing reasons, we reverse the rejection of claims 1-11, 13, 14, 16-32, 34, 37-46, and 48-50 under the enablement provision of 35 U.S.C. § 112, first paragraph.

Obviousness:

Claims 1-10, 13, 16-35, 37-46, and 48 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Zolotukhin, Sherf, Donnelly, Pan, Cornelissen, and Hey.

The claims are not argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Accordingly, we limit our discussion to claim 1.

Zolotukhin teaches “synthetic and ‘humanized’ versions of green fluorescent protein (GFP) genes adapted for high level expression in mammalian cells, especially those of human origin” (Zolotukhin Abstract). Zolotukhin teaches “humanized genes . . . definable by genes in which at least about 10% of said codon positions contain a humanized codon. That is, they contain a codon that is preferentially used in human genes in place of a codon that is not so frequently used in human genes” (Zolotukhin 2: 63-67). In addition, Zolotukhin teaches humanized genes that have at least “25%, about 30% or about 35% of the codon positions defined by the presence of a humanized codon” (Zolotukhin 3: 1-4). Zolotukhin also contemplates “[h]umanized gfp genes wherein at least about 50% or above of the codon positions contain a humanized codon” (Zolotukhin 3: 5-7).

The Examiner finds that Zolotukhin fails to teach a synthetic nucleic acid that has “at least 3-fold fewer transcription regulatory sequences than the parent nucleic acid” (Ans. 16). The Examiner relies on Sherf, Donnelly, Pan, Cornelissen, and Hey to make up for this deficiency in Zolotukhin

Sherf teaches “[a] modified form of beetle luciferase, which has been engineered for improved genetic reporting” (Sherf Abstract). Sherf teaches the removal of “potentially interfering restriction sites and genetic regulatory

sites from the gene [and the] improvement of the codon usage for mammalian cells” (*id.*). The Examiner finds that Sherf teaches the elimination of sequences “which encode transcription factor binding sites for know[n] mammalian transcription factors including ATF, AP1, Sp1, AP2[,] etc. which would interfere with its genetically neutral behavior” (Ans. 16). In addition, Sherf teaches the removal of “[t]hree palindromic sequences which could spuriously affect expression” (Sherf 9: 9-11). The Examiner finds that Sherf teaches an “altered gene [that] includes at least 6 fewer transcription factor binding sites” (Ans. 16-17).

The Examiner finds that Donnelly teaches a modified hepatitis C virus core antigen gene wherein the gene is optimized for human host cell codon usage, and also eliminates sequences which encode for “undesired sequences (such as ATTTA sequences, intron splice sites, etc.)” (Ans. 17)

The Examiner finds that Pan teaches a modified *Plasmodium falciparum* gene in which the codons are optimized for human host cells and sequences which might be detrimental to transcription (such as promoter sequences, “intron splice sites and long runs of purines which might act as transcriptional termination sequences”) are eliminated (*id.*).

The Examiner finds that Cornelissen teaches a modified *Bacillus thuringiensis* gene in which the codons are altered to eliminate sequences which, *inter alia*, might be detrimental to transcription including cryptic promoters or DNA regulatory elements (Ans. 18).

The Examiner finds that Hey teaches a plant sink protein gene in which the codons are optimized for plant host cells and wherein sequences which might be detrimental to transcription (including promoters, transcription factor binding sequences, intron splice sites, transcriptional

termination sequences and runs of 4 or more pyrimidines which might interfere with transcription) are eliminated (Ans. 18-19).

Based on the combined teachings of the prior art the Examiner concludes that it would have been obvious to further modify Zolotukhin's GFP gene to remove transcriptional regulatory sequences, including "potential promoter sequences, transcription binding factor sites, polyadenylation sites and splice sites" as taught by Sherf, Donnelly, Pan, Cornelissen, and Hey in order to optimize the expression of the GFP protein in host cells (Ans. 19).

In response, Appellants assert that none of the references relied upon by the Examiner teach 3-fold fewer transcriptional regulatory sequences relative to the number of such sequences in the parent nucleic acid sequence (*See generally* App. Br. 23-26). We are not persuaded. The combination of references relied upon by the Examiner suggest the removal of a variety of transcriptional regulatory sequences that may interfere with transcription in host cells. There is no evidence on this record that the removal of the transcriptional regulatory sequences suggested by Sherf, Donnelly, Pan, Cornelissen, and Hey from the gene taught by Zolotukhin would not result in a synthetic nucleic acid molecule that has at least 3-fold fewer transcription regulatory sequences relative to the number of such sequence in Zolotukhin's nucleic acid sequence.

We recognize Appellants' assertion that it is unclear from Sherf "why those alterations did not uniformly increase luciferase activity in all the tested mammalian cells" (App. Br. 23). We are not persuaded. The synthetic nucleic acid molecule of claim 1 need only encode a fluorescent polypeptide that has activity, it matters not according to claim 1 whether the

activity of the polypeptide is increased or decreased relative to the polypeptide encoded by the parent molecule.

We recognize Appellants' assertion that Cornelissen teaches that because only a relatively small number of modifications result in a substantial increase of foreign gene expression in plants, the modified genes produced in accordance with their invention are unlikely to contain newly introduced sequences that interfere themselves with expression of the gene in a plant cell environment (column 13, lines 33-42).

(App. Br. 25.) We are not persuaded. Cornelissen teach that bacterial genes, particularly BT ICP genes, may contain cis-acting regulatory elements in their coding regions "that seriously hamper the expression of these genes when they are introduced, under control of appropriate plant regulatory sequences . . . in a plant cell environment" (Cornelissen 13: 23-31). In this regard, Cornelissen teach that "[i]n general less than about 10% . . . nucleotide modifications in the coding region are required in order to substantially alleviate the expression problem" (Cornelissen 13: 33-36). Accordingly, while Cornelissen teaches the need to alter regulatory elements in a target gene to avoid expression problems; Cornelissen generalizes on the amount of modification necessary to substantially alleviate the problem associated with the expression of bacterial genes in a plant environment.

Contrary to Appellants' assertion, we do not find that Cornelissen is "opposite to those of the claimed invention" (App. Br. 25). A reference is said to "teach away" from a claimed invention when it "suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant" (*In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)). We do not find and Appellants have not identified a teaching in Cornelissen that would suggest that a modification of more than

10% of the coding regions of a target nucleic acid should be avoided or that a modification of less than 10% of the coding region *completely* alleviates the expression problem. Instead, we find only a generalized teaching that for bacterial genes, particularly BT ICP genes, the modification of less than about 10% of the coding region may be sufficient to substantially alleviate the expression problem. For the foregoing reasons we do not find that Cornelissen teaches away from Appellants' claimed invention.

On reflection, we find that the combination of references relied upon by the Examiner teach the claimed modified green fluorescent protein gene adapted for high level expression in a host cell, wherein the codons of the nucleic acid sequences differs from the parent molecule by at least 25% and wherein transcriptional regulatory elements that may interfere with the transcription of the resulting nucleic acid molecule are removed. There is no evidence on this record that the removal of the transcriptional regulatory sequences suggested by Sherf, Donnelly, Pan, Cornelissen, and Hey from the gene taught by Zolotukhin would not result in a synthetic nucleic acid molecule that has at least 3-fold fewer transcription regulatory sequences relative to the number of such sequence in Zolotukhin's nucleic acid sequence.

We are not persuaded by Appellants' assertion that there is no good reason why the skilled artisan with no knowledge of Appellant's disclosure would select to modify a fluorescent protein coding sequence, rather than a luciferase gene, hepatitis C virus gene, merozoite surface protein-1 gene, BT gene or sink protein gene, to reduce the number of TRS by replacing at least 25% of the codons, but not to reduce the number of glycosylation sites . . . , restriction endonuclease sites . . . , ATTTA sequences. . . , long runs of purines . . . , A and T

sequences . . . , or TA and CG doublets and blocks of G or C residues

(App. Br. 27.) There is no reason why a person of ordinary skill in the art would not change any or all of these sites in addition to the other sites taught by the combination of references relied upon. Claim 1 does not exclude the modification of these additional sites. Accordingly, we are not persuaded by Appellants' argument.

We are also not persuaded by Appellant's arguments regarding "the discredited 'obvious-to-try' standard" (App. Br. 28)

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product [is] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1742 (2007).

For the foregoing reasons we affirm the rejection of claim 1 under 35 U.S.C § 103(a) as unpatentable over the combination of Zolotukhin, Sherf, Donnelly, Pan, Cornelissen, and Hey. Since they are not argued separately, claims 2-10, 13, 16-35, 37-46, and 48 fall together with claim 1.

5. Claims 11, 14, 49, and 50 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Zolotukhin, Sherf, Donnelly, Pan, Cornelissen, Hey and any one of GenBank Accession No. AF406766, AY037768, or AY037769.

The claims are not argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Accordingly, we limit our discussion to claim 11.

Claim 11 depends from and further limits claim 1 to require that the synthetic nucleic acid molecule encodes a green fluorescent polypeptide that was derived from a nucleic acid molecule that was originally isolated from *Montastraea cavernosa*.

The Examiner relies on the combination of Zolotukhin, Sherf, Donnelly, Pan, Cornelissen, and Hey as discussed above (Ans. 20). The Examiner relies upon GenBank entries AF406766, AY037768, and AY037769 to “teach a gene encoding a green fluorescent protein from *Montastraea cavernosa*” (*id.*). Based on this evidence the Examiner concludes that “it would have been obvious to one of skill in the art to optimize the expression of the green fluorescent proteins of any of GenBank entries AF406766, AY037768, or AY037769 in human as taught by the combined disclosures of” Zolotukhin, Sherf, Donnelly, Pan, Cornelissen, and Hey (*id.*).

Appellants assert that

even assuming . . . that it would be obvious to try to prepare a synthetic nucleic acid having at least 3-fold fewer TRS, none of the cited documents explicitly teaches or suggests, or provides a motivation to prepare, Appellant’s synthetic nucleic acid molecules, e.g., those encoding a green fluorescent protein related to, or derived from a parent nucleic acid sequence encoding, a green fluorescent protein from *M. cavernosa*.

(App. Br. 30.) We are not persuaded. As discussed above, absent evidence to the contrary of which there is none, the combination of references relied upon by the Examiner teach a GFP nucleic acid molecule having a codon

that differs at more than 25% of the codons from a parent nucleic acid sequence encoding a fluorescent polypeptide, wherein the synthetic nucleic acid molecule has at least 3-fold fewer transcription regulatory sequences relative to the number of such sequences in the parent nucleic acid sequence. The GenBank references teach genes encoding a green fluorescent protein from *Montastraea cavernosa*. There is no evidence on this record to suggest that genes encoding a green fluorescent protein from *Montastraea cavernosa* could not be improved upon using the methodology set forth in the combination of references relied upon by the Examiner for expression in a host cell. *Cf. KSR*, 127 S. Ct. at 1740.

For the foregoing reasons we affirm the rejection of claim 11 under 35 U.S.C § 103(a) as unpatentable over the combination of Zolotukhin, Sherf, Donnelly, Pan, Cornelissen, Hey and any one of GenBank Accession No. AF406766, AY037768, or AY037769. Claims 14, 49, and 50 fall together with claim 11.

CONCLUSION

In summary, we affirm rejections 2, 4 and 5 and reverse rejections 1 and 3.

As a result of our deliberations, claims 12, 15, and 36 are free from rejection.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART

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cdc

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