Advanced Patent Prosecution Workshop 2021:

Claim Drafting & Amendment Writing

Biotechnology Answers for Homework Problem 1 and In-Class Problems 1-7

Table of Contents:

PLI Biotech Practice - Answer
Homework Problem 1

Docket No. XXX

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : Tough

Group Art Unit : XXXX

Applicants : Inventor et al.

Serial No. : 12/345,678

Filed : January 15, 2009

For : A NEW PROTEIN (VIP) USEFUL FOR TREATING PDQ RETROVIRUS INFECTIONS

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT UNDER 37 C.F.R. § 1.111

Sir:

In response to the June 1, 2012 Office Action, please amend the above-identified U.S. patent application as follows:

Amendments to the Specification begin on page 3 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 4 of this paper.

Remarks begin on page 9 of this paper.

It is believed that no fee is required for this response. However, should additional fees be necessary in connection with the filing of this response, or if a petition for extension of time is required for timely acceptance of the same, the Commissioner is

hereby authorized and requested to charge Deposit Account No. XXYY for any such fees, and applicants hereby petition for any needed extension of time.

AMENDMENT TO THE SPECIFICATION

Please replace the paragraph on page __, lines __, with the following replacement paragraph:

The supernatants from the 1000 XOX mutant clones were used as the test material in the above procedure. Untreated XBX cells were all dead (0% inhibition), as well as all cells on the plate receiving the parallel doses of the control protein, ovalbumin. The supernatants from five XOX mutant clones showed significantly greater antiviral activity in the XBX screening assay than the original XOX cell line supernatant. One mutant (designated 632E), producing the supernatant with the highest anti-viral activity (1000 times the starting XOX cell line supernatant), was selected for further Investigation. A cell line sub-cloned from the initial 632E clone was thereafter designated XOXE, ATCC accession No. 301,999, deposited December 8, 1998 with the ATCC.

CLAIM AMENDMENTS

1-12. (Canceled)

13. (New) An isolated nucleic acid having (or comprising) the nucleotide sequence of SEQ ID NO:1.

14. (New) An isolated and substantially purified viral inhibitory protein having the amino acid sequence of SEQ ID NO:2.

15. (New) An isolated nucleic acid having (or comprising) a nucleotide sequence that encodes the amino acid sequence of SEQ ID NO:2.

16. (New) An isolated nucleic acid having (or comprising) the nucleotide sequence of SEQ ID NO:3.

17. (New) An isolated nucleic acid having (or comprising) a nucleotide sequence that encodes the amino acid sequence of SEQ ID NO:4.

18. (New) An isolated nucleic acid having (or comprising) the nucleotide sequence of SEQ ID NO:5.

19. (New) An isolated nucleic acid consisting (essentially) of the nucleotide sequence of SEQ ID NO: 5.

20 . (New) An isolated nucleic acid having (or comprising) a nucleotide sequence that encodes the amino acid sequence of SEQ ID NO:6.

21. (New) An isolated nucleic acid consisting of the nucleotide sequence of SEQ ID NO:1 or a contiguous fragment thereof wherein said isolated nucleic acid encodes a polypeptide having the biological activity of viral inhibitory protein 1 or 2.

22. (New) An isolated nucleic acid that hybridizes under high stringency conditions to a nucleic acid having a sequence complementary to the nucleotide sequence of SEQ ID NO:1, wherein said isolated nucleic acid encodes a polypeptide having the biological activity of viral inhibitory proteins 1 and 2.

23. (New) An isolated nucleic acid consisting of the nucleotide sequence of SEQ ID NO:3 or a contiguous fragment thereof wherein said isolated nucleic acid encodes a polypeptide having the biological activity of viral inhibitory protein 1.

24. (New) An isolated nucleic acid that hybridizes under high stringency conditions to a nucleic acid having a sequence complementary to the nucleotide sequence of SEQ ID NO:3, wherein said isolated nucleic acid encodes a polypeptide having the biological activity of viral inhibitory protein 1.

25. (New) An isolated nucleic acid consisting of the nucleotide sequence of SEQ ID NO:5 or a contiguous fragment thereof wherein said isolated nucleic acid encodes a polypeptide having the biological activity of viral inhibitory protein 2.

26. (New) An isolated nucleic acid that hybridizes under high stringency conditions to a nucleic acid having a sequence complementary to the nucleotide sequence of SEQ ID NO:5, wherein said isolated nucleic acid encodes a polypeptide having the biological activity of viral inhibitory protein 2.

27. (New)An isolated nucleic acid consisting of a contiguous fragment of pCD-999 wherein said isolated nucleic acid encodes a polypeptide having the biological activity of viral inhibitory protein 1 or viral inhibitory protein 2.

28. (New) Isolated and substantially purified viral inhibitory protein having a specific anti-PDQ virus activity of at least 3000 IC50 units/mg protein.

29. (New) Isolated and substantially purified viral inhibitory protein 1 and 2 encoded by the nucleic acid of Claim 21.

30. (New) Isolated and substantially purified viral inhibitory protein 1 encoded by the nucleic acid of Claim 23.

31. (New) Isolated and substantially purified viral inhibitory protein 2 encoded by the nucleic acid of Claim 25.

32. (New) Isolated and substantially purified viral inhibitory protein having the amino acid sequence of SEQ ID NO:2, 4 or 6.

33. (New) A vector comprising the nucleic acid of Claim 13.

34. (New) A vector comprising the nucleic acid of Claim 15.

35. (New) A vector comprising the nucleic acid of Claim 17.

36. (New) A host cell comprising the nucleic acid of Claim 13.

37. (New) A host cell comprising the vector of Claim 33.

38. (New) A method of making viral inhibitory protein 1 or 2 comprising:

a) introducing the nucleic acid of Claim 21 into a host cell;

b) maintaining said host cell under conditions whereby said nucleic acid is expressed to produce viral inhibitory protein;

c) recovering said viral inhibitory protein.

39. (New) A method of making viral inhibitory protein 1 comprising:

a) introducing the nucleic acid of Claim 23 into a host cell;

b) maintaining said host cell under conditions whereby said nucleic acid is expressed to produce viral inhibitory protein;

c) recovering said viral inhibitory protein.

40. (New) A method of making viral inhibitory protein 2 comprising:

a) introducing the nucleic acid of Claim 25 into a host cell;

b) maintaining said host cell under conditions whereby said nucleic acid is expressed to produce viral inhibitory protein;

c) recovering said viral inhibitory protein.

41. (New) A method of making viral inhibitory protein 2 comprising:

a) culturing the host cell of claim 36 under conditions whereby said nucleic acid is expressed to produce viral inhibitory protein and

b) recovering said viral inhibitory protein.

42. (New) A composition comprising the purified viral inhibitory protein of claim 28 and a carrier.

43. (New) The composition according to claim 42 which further comprises viral inhibitory protein 2.

44. (New) A method of inhibiting PDQ virus comprising contacting a cell infected with PDQ virus with the composition of claim 42.

45. (New) An isolated mutein of the viral inhibitory protein or fragment thereof of claim 28, having a specific activity of at least about 3500 IC50 units/mg.

46. (New) The isolated mutein of claim 45 having an amino acid change at position 20.

47. (New) The isolated mutein of claim 46, wherein said amino acid change is Pro or Leu.

48. (New) The isolated mutein of claim 45 having an amino acid change at position 23.

49. (New) The isolated mutein of claim 48, wherein said amino acid change is Glu or Leu.

50. (New) An isolated mutein of claim 45 having an amino acid change at position 23 and at position 78.

51. (New) The isolated mutein of claim 50 wherein said amino acid change at position 23 is Pro or Leu and said amino acid change at position 78 is Ala or Leu.

52. (New) A truncated viral inhibitory protein of claim 28 wherein the first five C-terminal or N-terminal amino acids of said viral inhibitory protein are missing.

53. (New) A complex comprising an isolated and substantially purified viral inhibitory protein having the amino acid sequence of SEQ ID NO:2 and an isolated and substantially purified viral inhibitory protein having the amino acid sequence of SEQ ID NO:4.

54. (New) A method for detecting anti-PDQ viral activity in a sample comprising detecting the presence or absence of VIP1 or VIP2 activity.

REMARKS

Applicants have enclosed a Revocation of Power of Attorney and a new Power of Attorney executed by the assignee of interest, and a statement under 37 C.F.R. §3.73(b).

Applicants have amended the specification to insert the ATCC accession number for cell line XOXE. Applicants request that the amendment to the specification be entered. No new matter is added.

Applicants have also canceled claims 1-12 without prejudice and have replaced them with new claims 13-54. These amendments are fully supported by the original disclosure in the specification. see, e.g., page , line , through page , line . Applicants request that these amendments be entered and the amended claims allowed.

REJECTION UNDER 35 U.S.C. § 101

The Examiner rejected claims 1 and 2 under 35 U.S.C. § 101 as directed to non-statutory subject matter. In response, to more specifically point out the claimed invention and exclude VIP and its DNA as they occur in nature, Applicants have canceled claims 1 and 2 and introduced new claims 13-54. The new claims, particularly, new claims 13-35 and 45-51 are directed to isolated nucleic acid or protein sequences.

Claims 2, 4, 6, and 9 have been rejected under 35 U.S.C. §101 because the claimed invention is not supported by a well established utility. In the Examiner's view, there is no disclosed or real world utility associated with the claimed protein or protein encoded by the claimed DNA sequence. Applicants respectfully traverse the rejection. In the Applicant's view, a "real world" utility is indeed disclosed. The utility guidelines require that an applicant assert a specific and substantial utility that is credible. All three criteria have been met. Two utilities of VIP2 are disclosed: it binds to VIP1 and the specific activity of VIP1/VIP2 is greater than VIP1. Both of these utilities are substantial and credible. Certainly, acting as an antiviral agent is credible.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner has objected to the specification under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way to enable one skilled in the art to which it pertains to you use the invention.

The Examiner cites United States v. Teletronics and In re Wands to set out the standard of undue experimentation and the factors to be considered in the determination of enablement. The Examiner has also rejected also claims 1-12 under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Applicants traverse this rejection. New claims 13-54 have been added. Applicants point out that the composition claims now relate to an isolated and substantially purified viral inhibitory protein (VIP), an isolated nucleic acid encoding VIP, vectors, host cells and compositions. New claims 13-54 also are directed to a method of making VIP, a method of inhibiting PDQ virus, and a method of screening for anti-PDQ viral activity. Applicants submit that the presently claimed invention meets the requirements of § 112, paragraph one.

A patent applicant's specification disclosure which contains a teaching of how to make and use the invention must be taken as enabling unless the Patent Office provides sufficient reason to doubt the accuracy of the disclosure. *In re Marzocchi*, 439 F.2d 220, 223-224 (C.C.P.A. 1971); *In re Brana*, 34 U.S.P.Q.2d 1437, 1441 (Fed. Cir. 1995). The Examiner has come forward with no objective evidence to support his contention that the present compositions and methods, as described in the specification, could not be made and used as described by one of skill in the art.

The allegations of utility made by Applicants are not, and do not border on the incredible, in view of the experimental data presented in the application. The utility put forth by Applicants is credible to one of skill in the art, thus satisfying the requirements under § 112.

Applicants point out that the specification at page 7 describes experiments performed to determine the ability of the VIP protein to inhibit PDQ virus. Applicants also note that enablement does not require optimal efficacy, only some efficacy.

Applicants maintain that the *in vitro* assay used by Applicants to demonstrate the anti-PDQ viral activity of the claimed compounds is predictive of *in vivo* activity. See, e.g., Jones et al., The Journal, June, 1995, pp. 440-494. Jones demonstrates that Applicants' *in vitro* results do, in fact, correlate to in vivo activity. Jones tested three compounds known to produce an antiviral effect *in vivo* in PDP-infected monkeys in the very same *in vitro* model used by Applicants (i.e., XBX cells). Jones demonstrated that

the three compounds inhibited viral progression in the *in vitro* model -- just as it had *in vivo*. PDP-virus in monkeys is an analogous virus to PDQ in humans. Both viruses are, in fact, transactivated by MTV. Accordingly, one skilled in the art would be convinced that Applicants' results with VIP (and its muteins and truncated forms) *in vitro* in XBX cells are indicative of VIP's utility in treating PDQ viral infection *in vivo*. Thus, Jones clearly demonstrates that Applicants' *in vivo* results do in fact correlate with *in vivo* utility.

The Examiner has rejected claims 1-6 and 11-12 under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification. The Examiner contends that the disclosure in the present specification of 8 proteins (VIP, 3 muteins and 4 truncated versions) and the DNA sequences encoding these proteins is inadequate to support the breadth of the pending claims. Applicants traverse.

The specification provides adequate support for the claims. First, the application teaches how to make eight (8) specific proteins all of which fall within the scope of the claims. See page , line through page , line . Second, the application teaches how other muteins and truncated VIP's can be made and identified without undue experimentation. See, e.g., the assays disclosed on page , lines . There can be no doubt that one of skill in the art could follow these teachings to make other proteins that would fall within the claims. And, the Examiner has pointed to none. [This argument could be beefed up by adding Forman and going through each of the factors.] Accordingly, the specification is fully commensurate in scope with the claims.

Claims 1, 2, 5, 6 and 11 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description in the specification. The Examiner has alleged that the claimed DNA is described in generic terms, and the skilled artisan could not envision the subgenus of DNA molecules that meets the claim limitations.

Claims 13-27 recite nucleic acid molecules described in terms of function, nucleic acid sequences, ability to hybridize to nucleic acids of defined sequences. Applicants submit that adequate written description for the claimed subject matter is present in the specification, for example at _____.

Recitation of a sequence of nucleotides is sufficient to meet the written description requirement of 35 U.S.C. §112, first paragraph. University of California v.

Eli Lilly and Co. 43 U.S.P.Q. 2d 1398, 1406 (Fed. Cir. 1997). Applicants submit that a description of nucleic acids that are capable of hybridizing to a defined sequence, or that have a certain percent identity to a defined sequence, similarly meets the written description requirement. Such a description specifically defines the nucleic acids within the scope of the claims in that it conveys to one of skill in the art that applicants had possession of the claimed invention.

Claim 10 stands rejected under 35 U.S.C. § 112, first paragraph, as being based on insufficient enabling disclosure in the specification and for failure to satisfy the best mode requirement. The Examiner asserts that there is insufficient disclosure in the specification to support the breadth of this claim and that deposit of mutant cell line XOXE is required to meet the best mode requirement. Applicants traverse.

The application meets both the how to make and how to use requirements of 35 U.S.C. § 112. The specification clearly teaches how to make mutants of the XOX cell line, a commercially available cell line. See page _____, lines _____, where the details are disclosed of how the original XOX cells are treated to obtain the mutants. See also page _____, lines _____, where the specification teaches in detail the assay for identifying positive mutants. As pointed out in the specification, Applicants identified five different XOX mutant clones using these very procedures. Each had significantly greater anti-viral activity than the original XOX cell line. Lastly, see page _____, lines _____, where the specification teaches how to use such the claimed mutant cell line to recombinantly produce a useful protein-VIP. In sum, the specification teaches how to make the mutants, how to identify the desired mutants, and how to use the mutants to produce a desired utility. For the same reasons, the application also discloses the best mode of making the mutant XOX cell line.

However, to expedite prosecution of this application, Applicants have deposited mutant cell line XOXE. Applicants have also amended the application to add the ATCC accession number for this XOXE cell line. See, page , line .

Cultures of the following biological materials were deposited with the American Type Culture Collection (ATCC) in Manassas VA under conditions to satisfy the Budapest Treaty (a copy of the acknowledgement letter stating the terms of the deposit is attached),

Designation of Organism	Accession Number	Date of Deposit
Cell line designated XOXE, producing a protein designated VIP which is capable of inhibiting MTV-activation of PDQ virus.	301,999	8 December 1998

The undersigned hereby assures the United States Patent and Trademark Office and the public that (a) all restrictions on the availability to the public of the cell line above will be irrevocably removed upon issuance of a United States patent of which such cell line are the subject; (b) the cell line will be maintained for a period of at least five years after the most recent request for the furnishing of a sample of the deposited cell line was received by the ATCC and, in any case for a period of at least 30 years after the date of deposit; (c) should the deposit become non-viable it will be replaced by the Applicants and (d) access to the cell line will be available to the Commissioner during the pendency of the patent application or to one determined by the Commissioner to be entitled to such vectors under 37 C.F.R. § 1.14 and 35 U.S.C. § 122.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner rejected claims 1-12 (now claims 13-54) under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Examiner criticizes the use the terms "VIP", "anti-viral activity", "anti-virally effective amount", "biological equivalent", "increased amounts", "up toll, "anti-viral activity", "MTV-inhibition", “capable of” and "MTV-activation".

Other than "VIP", the above terms have been clarified in the newly submitted claims. Applicants submit that "VIP" is fully defined in the specification and would clearly be understood by one of ordinary skill, see page , line . This is supported at page , line . See page ,line . The term “capable of” is not used in the new claim submitted.

In view of these clarifications, all of the new pending claims meet the definiteness requirement of 35 U.S.C. § 112.

REJECTION UNDER 35 U.S.C. § 102(b)

Claims 1-4 and 9 (now claims 13-37 and 44) stand rejected under 35 U.S.C. § 102(b) as being anticipated by Anglin et al. Applicants traverse.

Claims 13-37 and 44 now relate to purified VIP having a specific anti-PDQ virus activity of at least 3500 IC50 units/mg protein and to isolated and purified DNA constructs encoding such proteins. Anglin does not disclose such a purified protein or an isolated and purified DNA construct. Accordingly, it does not anticipate any of these claims.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 5-8 (now claims 38-43) stand rejected under 35 U.S.C. § 103 as being obvious over Anglin. The Examiner argues that Anglin teaches that XOX cell supernatants contain a protein useful in the treatment of PDQ viral infection. He then asserts that it would have been obvious to one skilled in the art to purify the protein by well-known techniques such as HPLC (or to make it by recombinant means) and use the protein for the purposes described in Anglin. Applicants traverse.

Anglin itself teaches away from Applicants' invention and the Examiner's contention of how it could be made. Anglin reported that a polypeptide was in the supernatant from XOX cells in very low concentration and that they were unable to purify the protein to homogeneity. Only Applicants' invention of creating mutant XOX cells which produce significantly higher amounts of VIP made it possible to isolate to cleave and identify the DNA sequence encoding it. Thus, VIP and the DNA encoding it could not have been (and were not) obvious from the Anglin. In sum, the Anglin just does not provide any reasonable expectation that the isolation of VIP or of the gene encoding it would be successful in advance of Applicants' invention.

Respectfully submitted,

_____

YOUR NAME
Reg. No. XXXXX
Attorney for Applicants
Address
Telephone No.

PLI Biotech Practice - Answers
In Class Problem 1

The claims cover both fully human antibodies (i.e., antibodies with human variable and constant regions) and chimeric antibodies. In *Centocor v. Abbott Labs*, 636 F.3d 1341 (2011), the Federal Circuit found the claims lacked written description since the inventors described the problems associated with obtaining fully human antibodies, and only showed possession of chimeric antibodies. The Court pointed out that the specification of the patent "does not disclose any relevant identifying characteristics for such fully human antibodies or even a single human variable region. Nor does it disclose any relationship between the human TNF-α protein, the known mouse variable region that satisfies the critical claim limitations, and potential human variable regions that will satisfy the claim limitations."

The Federal Circuit also clarified the antibody exception:

> The antibody example presumes that the applicant is disclosing a novel protein and then claiming both the protein and an antibody that binds to it.
>
> An applicant can claim an antibody to novel protein X without describing the antibody when (1) the applicant fully discloses the novel protein and (2) generating the claimed antibody is so routine that possessing the protein places the applicant in possession of an antibody.

If the patent application was filed in 2015, there is a greater likelihood that the claims would satisfy the written description requirement as there are many known techniques for preparing fully human antibodies.

PLI Biotech Practice - Answers
In Class Problem 2

There is no case on this question yet. There, however, are good arguments for the claims satisfying section 101. The *Association for Molecular Pathology v. Myriad Genetics* decision looked at, *inter alia*, whether isolated DNA from a chromosome had a "distinctive name, character [and] use." The oligonucleotide appears to have different biological activity and uses (inducing growth of eyelashes) then the natural gene which includes it (which causes unusually large eyes). This is evidence that the oligonucleotide is markedly different from the natural products in name, character, and use. *Diamond v. Chakrabaty*, 447 U.S. 303, 309-310 (1980).

PLI Biotech Practice - Answers
In Class Problem 3

In *Scantibodies Lab., Inc. v. Immutopics, Inc*., 374 Fed. Appx. 968 (unpublished) (Fed. Cir. 2010), the Federal Circuit found that the terms “specific for” and “not detecting an interfering non-(1-84) parathyroid hormone fragment” meant that the labeled antibody had absolutely no cross-reactivity with interfering non-(1-84) parathyroid hormone fragment. The Court blamed the inventors for the narrow claim language:

> the inventors of the '566 patent chose to draft the claims with the narrow term "not detecting" when there were alternatives that were less confining. If the inventors wanted "not detecting" to have a different meaning based on the clinical or marketing context, they could have drafted the claims differently. For example, the inventors could have chosen a term with a broader meaning or have assigned "not detecting" a unique definition different than its ordinary meaning by clearly expressing that intent in the written description. … Here, the inventors elected to do neither. Because of this choice, a competitor reading the '566 patent would not know that "not detecting" means something other than its ordinary meaning and would not be forewarned that it might infringe.

The Federal Circuit also pointed out that the inventors had published an article disclosing one such antibody that exhibited no cross-reactivity. As the defendants antibody exhibited cross-reactivity, the Court affirmed the lower court’s finding of no infringement.

PLI Biotech Practice - Answers
In Class Problem 4

In *Enzo Biochem, Inc. v. Applera Corp*., 599 F.3d 1325 (Fed. Cir. 2010), the phrase "does not substantially interfere with" was held to be definite under 35 U.S.C. §112, second paragraph (pre-AIA). The Court stated:

> We begin with the language of the claims. The word "substantially," when used in a claim, can denote either language of approximation or language of magnitude. *See* *Deering Precision Instruments, LLC v. Vector Distrib. Sys., Inc.*, 347 F.3d 1314, 1323 (Fed.Cir.2003). As used in the phrase "not interfering substantially," the word "substantially" denotes language of magnitude because it purports to describe *how much* interference can occur during hybridization, i.e., an insubstantial amount of interference. *See* *Epcon Gas Sys., Inc. v. Bauer Compressors, Inc.*, 279 F.3d 1022, 1031 (Fed.Cir.2002) ("[T]he phrase `substantially]below' signifies language of magnitude, i.e., not insubstantial."). The claims in this case provide at least some guidance as to how much interference will be tolerated. A dependent claim in both patents specifies that the linkage group has a particular structure (-CH=CH-CH_2-NH-). *See* '824 patent col.32 ll.66-68; '767 patent col.31 ll.38-40. A person of ordinary skill would presume that a structure recited in a dependent claim will perform a function required of that structure in an independent claim. *See* *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1242 (Fed.Cir.2003) ("Under the doctrine of claim differentiation, dependent claims are presumed to be of narrower scope than the independent claims from which they depend."). Thus, it may be presumed that the term "not interfering substantially" in the independent claims allows for at least as much interference as that exhibited when the linkage group has the structure specified in the dependent claims.
>
> The specification provides additional examples of suitable linkage groups, including some criteria for selecting them. After stating generally that the linkage group "may include any of the well known bonds including carbon-carbon single bonds, carbon-carbon double bonds, carbon-nitrogen single bonds, or carbon-oxygen single bonds," the specification goes on to note that "[i]t is even more preferred that the chemical linkage group be derived from a primary amine, and have the structure -CH2-NH-, since such linkages are easily formed utilizing any of the well known amine modification reactions." '824 patent col.8 ll.54-58, col.9 ll.1-5. Moreover, one of the "essential criteria" of a modified polynucleotide noted in the specification is that "the linkage that attaches the probe moiety should withstand all experimental conditions to which normal nucleotides and polynucleotides are routinely subjected, e.g., extended hybridization times at elevated temperatures, phenol and organic solvent extraction, electrophoresis, etc." *Id.* col.6 l.29, col.7 ll.3-8.
>
> The specification also teaches that the polynucleotides' "thermal denaturation profiles and hybridization properties" can be used to measure the degree to which a linkage group

interferes with hybridization. *Id.* col.18 ll.61-62. Because hybridization occurs via hydrogen bonding between complementary bases, any interference in this bonding will result in weaker intermolecular forces and thus a lower melting temperature (Tm) of the hybrid. For example, the specification states that a DNA strand was modified by substituting every thymidine residue of the strand with a biotinyl-nucleotide. The resultant hybridization exhibited by the modified DNA strand was reported to be acceptable: "the Tm is *only* 5 °C less than that of the unsubstituted control." *Id.* col.19 ll.5-8 (emphasis added). A similar test was performed on poly d(A-bioU), in which every base pair contained a bio-dUMP residue. This modified polynucleotide showed a significantly lower Tm than the unsubstituted control, yet its hybridization was still deemed acceptable: 1335*1335 "Although the Tm ... is 15 °C lower than the poly d(A-T) control, the *degree of cooperativity and the extent of hyperchromicity* observed both during denaturation and renaturation *were the same* for the two polymers." *Id.* col.19 ll.9-14 (emphases added). Thus, as a general guideline, when a linkage group is incorporated into a DNA strand having a length and sequence similar to those used in the specification, a decrease in Tm of up to 5 °C implies that the linkage group does not "substantially interfere" with hybridization, and a decrease of up to 15 °C is acceptable if the degree of cooperativity and the extent of hyperchromicity are the same for the modified and unmodified strands.

The prosecution history of these patents is also helpful. Before the U.S. Patent and Trademark Office ("PTO"), Enzo overcame an indefiniteness rejection over the "not interfering substantially" language by submitting a declaration under 37 C.F.R. § 1.132, which was signed by its vice president, Dr. Engelhardt ("Engelhardt Declaration"), listing eight specific linkage groups that Enzo declared did not substantially interfere with hybridization or detection. Among the named linkage groups was -CH=CH-CH2-NH(the same group recited in the patents' dependent claims) and -NH-(CH2)6-NH(a new group that is not found in the specification and which contains only single bonds). J.A. 4320. Based on this submission, the examiner withdrew the indefiniteness rejection.

Because the intrinsic evidence here provides "a general guideline and examples sufficient to enable a person of ordinary skill in the art to determine [the scope of the claims]," *In re Marosi,* 710 F.2d 799, 803 (Fed.Cir.1983), the claims are not indefinite even though the construction of the term "not interfering substantially" defines the term without reference to a precise numerical measurement, *see Young,* 492 F.3d at 1346 (holding that a word of degree was definite, even without a numerical claim construction); *Exxon,* 265 F.3d at 1381 (same);*Marosi,* 710 F.2d at 803 (same); *In re Mattison,* 509 F.2d 563, 565 (CCPA 1975) (same). When deciding whether a particular linkage group is or is not "substantially" interfering with hybridization within the meaning of the district court's construction, a person of ordinary skill would likely look to the thermal denaturation profiles and hybridization properties (including Tm) of the modified nucleotide, to see whether they fall within the range of exemplary values disclosed in the intrinsic evidence. *See Young,* 492 F.3d at 1346 (stating that a figure in the specification "provides a standard for measuring the meaning of the term `near,'" even without a numerical claim construction); *Exxon,* 265 F.3d at 1380 (stating that a "period sufficient," recited in the claim, can be ascertained by performing activity checks).

Contrary to Applera's assertion, the fact that the binding strength of a DNA strand may vary, based on the length and sequence of the strand, does not mean that the choice of a linkage group will "depend solely on the unrestrained, subjective opinion of a particular individual purportedly practicing the invention," as in *Datamize.* 417 F.3d at 1350. In *Datamize,* the invention was directed to a computer interface screen with an "aesthetically pleasing look and feel." *Id.* at 1344-45. The patentee sought a construction of the term "aesthetically pleasing" that depended solely on the subjective opinion of the person selecting features to be included on the interface screen. Nothing in the intrinsic evidence provided any guidance as to what design choices would result in an "aesthetically pleasing" look and feel. *Id.* at 1352. The claims were held indefinite because the very same interface screen may be "aesthetically pleasing" to one user but not to another.

Here, by contrast, the binding strength of a DNA strand will depend on the length and sequence of the strand, not on the subjective opinion of the particular chemist performing the hybridization. This is because, under a given set of experimental conditions, a DNA strand of a given length and sequence will have a fixed, measurable denaturation profile, which can be compared with the examples in the specification to determine whether interference with hybridization is substantial. The claims are not indefinite simply because the binding strength of a DNA strand will vary based on the strand's length and sequence. *See Young,* 492 F.3d at 1346 (holding claim definite even though "the size of the appendage and the amount of skin required to be incised will vary from animal to animal based on the animal's size").

Thus, we hold that the claim language regarding "hybridization" is not indefinite.

With regard to "detection," we agree with Enzo that the claims are not indefinite for most of the same reasons discussed in connection with "hybridization." The eight linkage groups listed in the Rule 132 declaration were said not to "interfere[] with the ability of biotin in an oligo- or polynucleotide probe of this invention to form a detectable complex with one of avidin, streptavidin or antibodies to biotin or iminobiotin." J.A. 4318. According to the specification, when biotin is used as the moiety A, the resultant complexes can be detected "by means of conventional detection techniques." '824 patent col. 18 ll.4-6. So long as moiety A can be detected within the level of detection achieved by the applicants using the exemplary linkage groups disclosed in the intrinsic evidence, a person of ordinary skill would understand that a different linkage group (one that is not disclosed in the intrinsic evidence) likewise does not "substantially interfere" with the detection of moiety A. The claims are not indefinite even if some experimentation is required to determine the exact level of detection achieved by the applicants using their exemplary linkage groups. *See Exxon,* 265 F.3d at 1379 ("Provided that the claims are enabled, and no undue experimentation is required, the fact that some experimentation may be necessary to determine the scope of the claims does not render the claims indefinite.").

PLI Biotech Practice - Answers
In Class Problem 5

In *Carnegie Mellon University v. Hoffmann-La Roche*, 541 F.3d 1115 (Fed. Cir. 2008), the Federal Circuit found the claim invalid for lack of written description for bacterial sources other than *E. coli*.

> The appealed claims of the '708 patent are directed to recombinant plasmids that contain a DNA coding sequence that is broadly defined, and only by its function, *viz.,*encoding DNA polymerase I. Moreover, the generic claims are not limited to a single bacterial species, but broadly encompass coding sequences originating from *any* bacterial species. …
>
> In *Eli Lilly,* we held that "the claimed genera of vertebrate and mammal cDNA [were] not described by the general language of [a] patent's written description supported only by the specific nucleotide sequence of rat insulin." 119 F.3d at 1569. That holding was premised on the basic principle that a person of skill in the art must be able to "visualize or recognize the identity of the members of the genus." *Id.* Thus, to satisfy the written description requirement for a claimed genus, a specification must describe the claimed invention in such a way that a person of skill in the art would understand that the genus that is being claimed has been invented, not just a species of the genus.
>
> The Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112, ¶ 1, "Written Description" Requirement, 66 Fed.Reg. 10-99 (Jan. 5, 2001) ("Guidelines"), which we find to be an accurate description of the law by the agency responsible for examining patent applications, and thus persuasive authority, provide further guidance for determining whether the written description requirement is met for claims drawn to a genus. The Guidelines state:
>
> > The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species ... by disclosure of relevant, identifying characteristics, *i.e.,* structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.
> > A "representative number of species" means that the *species which are adequately described are representative of the entire genus.* Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.
> > * * *
> > Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the

> necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot be achieved by disclosing only one species within the genus.*

Guidelines, 66 Fed.Reg. at 1106 (emphases added).

Here, while the claims of the '708 [patent] encompass a genus of recombinant plasmids that contain coding sequences for DNA polymerase or nick-translation activity from any bacterial source, in contrast, the narrow specification[] of the '708 [patent] only disclose[s] the *polA* gene coding sequence from one bacterial source, *viz., E. coli.* Significantly, the specification fails to disclose or describe the *polA* gene coding sequence for any other bacterial species.

The district court concluded that the disclosure of the *E. coli polA* gene was not representative of and failed to adequately support the entire claimed genus. Based on the record evidence indicating a lack of a genuine issue of material fact on the issue, we agree. Notably, the record indicates that at the time of the invention, only three bacterial *polA* genes,*viz., E. coli, K. aerogenes,* and *K. pneumoniae,* out of thousands of bacterial species had been cloned, and only *E. coli* was described in the patents. According to Roche's expert, Dr. Bambara, bacteria constitute a large class of organisms that include thousands, and potentially millions, of unidentified species. In addition, at the time of the invention, persons of ordinary skill in the art knew that DNA polymerase I was not a single enzyme, but a family of enzymes encoded by a family of genes that varied from one bacterial species to another. Dr. Bambara stated that those enzymes were encoded by genes that were distinct from the *E. coli polA* gene.

Significantly, the written description[] of the '708 [patent] clearly indicate[s] that the *polA*gene is critical to the claimed invention. Indeed, the patents disclose that a "significant discovery of the present invention" involved the need to severely damage the *polA* promoter sequence when constructing the recombinant plasmid in order to avoid the unregulated expression of DNA polymerase I, which otherwise would be lethal to the cell. '708 patent col.2 ll.40-46. The specifications disclose that "[t]he novel plasmid of the present invention contains the entire and undamaged *polA* gene coding region enzymatically excised from a DNA molecule" and emphasize that "it is an important feature of this invention that the cloned *polA*gene fragment contains essentially none of or at the most only a portion of the activity of its natural promoter." *Id.* col.2 ll.23-29.

However, although the written descriptions of the patent[] emphasize[s] that the recombinant plasmids must be carefully constructed in order to overcome the lethality problem, particularly with regard to the promoter, the patent[] fail[s] to disclose the nucleotide sequence or other descriptive features for a *polA* gene (including the promoter sequence) from any bacterial source other than *E. coli.* Indeed, in the Description of the Preferred Embodiments, the patent[] disclose[s] only one embodiment which uses the plasmid referred to as pMP5. …

We agree with the district court that the narrow disclosure of the *E. coli polA* gene is not representative of and fails to adequately support the entire claimed genus under *Eli Lilly*. To satisfy the written description requirement in the case of a chemical or biotechnological genus, more than a statement of the genus is normally required. One must show that one has possession, as described in the application, of sufficient species to show that he or she invented and disclosed the totality of the genus. In light of the specifications' disclosure concerning the careful construction of the claimed recombinant plasmids, such that the natural promoter of the *polA* gene is severely damaged or eliminated, and given the record evidence that the *polA* gene varied among the numerous bacterial species, as well as the absence of any *polA* gene sequence for any bacteria other than *E. coli,* we conclude that that requirement was not met here.

PLI Biotech Practice - Answers
In Class Problem 6

In *Monsanto v. Syngenta Seeds*, 503 F.3d 1352 (Fed. Cir. 2007), the Court found no infringement since the SAC (Syngenta) did not perform the process of claim 1, from which claims 4-9 depend:

> According to § 112, ¶ 4, claims in dependent form include all the limitations of the claim incorporated by reference into the dependent claim. On appeal, Monsanto concedes that Syngenta has not infringed independent claim 1 of either Lundquist patent. Nevertheless, Monsanto insists that Syngenta infringed claims 4-9 of the '880 patent and claims 5-6 of the '863 patent. To reach this conclusion, Monsanto contends that, even if the asserted claims of the Lundquist patents are dependent claims, Syngenta should still be liable for infringing them, because each limitation of the independent claims of the Lundquist patents have been performed (albeit by Monsanto's own subsidiary Dekalb). Alternatively, Monsanto contends that, even if the asserted claims of the Lundquist patents are dependent claims, Syngenta should still be liable for infringing them, because Syngenta infringes any "four-step" claimed process by completing the last step of "obtaining progeny" during the patent term (albeit with the first three steps occurring before the patents issued).
>
> Monsanto's first argument cannot prevail in light of this court's decision in *Wahpeton Canvas Co., Inc. v. Frontier, Inc*., 870 F.2d 1546, 1552 (Fed. Cir. 1989). In *Wahpeton,* this court explained:
>
> > One may infringe an independent claim and not infringe a claim dependent on that claim. The reverse is not true. One who does not infringe an independent claim cannot infringe a claim dependent on (and thus containing all the limitations of) that claim.
>
> *Id.*
>
> According to Monsanto, the district court misconstrued *Wahpeton* as holding that dependent claims cannot be "infringed" unless someone would be liable for infringing the independent claims from which they depend. Monsanto urges that *Wahpeton* only applies when the accused product or process lacks a limitation present in the independent claim, but not when all the independent limitations are missing. The *Wahpeton* rule typically applies in cases where the accused product or process lacks a single limitation from the independent claim. The rule does not change, however, where all of the steps of the independent claim are missing. In the present case, *no one* performed the three-step process of the independent claim "during the patent term," as required by § 271(a). Indeed, Monsanto itself (through Dekalb) practiced the three-step process before the '863 and '880 patents issued.

Monsanto's second argument is also inconsistent with the basic rule for infringement. As this court has stated many times, "[f]or infringement of a process invention, all of the steps of the process must be performed, either as claimed or by an equivalent step." *EMI Group N. Am., Inc. v. Intel Corp.,* 157 **F.3d** 887, 896 (Fed.Cir.1998). As a result of this rule, the performance of the three steps (of independent claim 1) is a *prerequisite* for the infringement of the four-step process claims of the Lundquist patents. Furthermore, infringement under § 271(a) requires use "without authority . . . during the patent term."

This case lacks any basis for infringement under claim 1 because those steps occurred before patent issuance. Monsanto itself performed those three steps before issuance of the Lundquist patents. Thus, Monsanto itself authorized the first three steps of the claimed four-step process. Thus, this court finds no error in the district court ruling as to the claim of infringement under § 271(a). Further, this court reaches the same result with respect to Monsanto's claim of infringement under § 271(g). Infringement is not possible under § 271(g) when the three first steps of the claimed process are performed before the issuance of the patent. In *Mycogen Plant Science, Inc. v. Monsanto Co.,* this court held that § 271(g) "requires that the patent be issued and in force at the time that the process is practiced and the product is made." 252 F.3d 1306, 1318 (Fed. Cir.2001) (finding no § 271(g) infringement where all process steps were practiced and product was made before patent issued),*vacated on other grounds,* 535 U.S. 1109, 122 S.Ct. 2324, 153 L.Ed.2d 153 (2002). This court explained "[b]ecause domestic entities do not infringe a process patent if they practice the process before the beginning of the patent term, even if they sell the products of the process during the term of the patent, parallel treatment of overseas entities indicates that the statute does not reach pre-issuance use of the later-patented process." *Id.* (citation omitted). Further, in *Joy Technologies, Inc. v. Flakt, Inc.,* this court explained that a method or process claim is directly infringed only when the process is performed. 6 F.3d 770, 774 (Fed. Cir. 1993). Thus, infringement of a multi-step method claim cannot lie by the performance of a single step after issuance of the patent when the initial steps were performed prior to issuance. Therefore, this court affirms the district court's judgment that Syngenta's products do not infringe claims 4-9 of the '880 patent and claims 5-6 of the '863 patent. Syngenta cannot be liable under § 271(a) or (g).

PLI Biotech Practice - Answers
In Class Problem 7

The CAFC, in *In re Hubbell*, 709 F.3d 1140 (Fed. Cir. 2013), held that obviousness-type double patenting does indeed apply when an application and a patent have one or more inventors in common but inventive entities are not identical and the application and the patent were never commonly owned. The court at p. 9 cited MPEP 804(I)(A):

> "[d]ouble patenting may exist between an issued patent and an application filed by the same inventive entity, or by a *different inventive entity having a common inventor*, and/or by a common assignee/owner." [emphasis added]

The court took judicial notice of MPEP 804(I)(A) to conclude that common ownership is not required and that obviousness-type double patenting applied since the '685 patent and the '509 application had two common inventors.

The court also held that a terminal disclaimer could not be filed to overcome the obviousness-type double patenting rejection. The court at p. 14 citing 37 C.F.R. § 1.321(c)(3) that a terminal disclaimer

> "filed to obviate judicially created double patenting in a patent application" must include "a provision that any patent granted on that application . . . shall be enforceable only for and during such period that said patent is *commonly owned* with the application or patent which formed the basis for the judicially created double patenting." [emphasis added]

Since the '685 patent and the '509 application were not commonly owned, filing of a terminal disclaimer was not possible.