

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 16

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte CHARLES A. MCWHERTER, YIQING FENG
JOHN P. MCKEARN, NICHOLAS R. STATEN, PHILIP R. STREETER,
SUSAN L. WOULFE, NANCY I. MINSTER, and JOHN C. MINNERLY

Appeal No. 2001-1580
Application No. 08/955,090

ON BRIEF

Before WILLIAM F. SMITH, MILLS, and GRIMES, Administrative Patent Judges.
GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-11, all of the claims in the application. Claim 1 is representative and reads as follows:

1. A human flt-3 receptor agonist polypeptide, comprising a modified flt-3 ligand amino acid sequence selected from the group consisting of:

(a) the sequence of SEQ ID NO:144; and

(b) a polypeptide comprising residues 1-132 of SEQ ID NO:144;

wherein said modification comprises the linear rearrangement of the sequences of (a) or (b); wherein the N-terminus is joined to the C-terminus directly or through a linker capable of joining the N-terminus to the C-terminus and new C- and N-termini are created between the amino acid residue pairs of SEQ ID NO:144 selected from the group consisting of:

28-29, 29-30, 30-31, 31-32, 32-33, 34-35, 36-37, 37-38, 38-39, 40-41, 41-42, 42-43, 64-65, 65-66, 66-67, 86-87, 87-88, 88-89, 89-90, 90-91, 91-92, 92-93, 93-94, 94-95, 95-96, 96-97, 97-98, 98-99, 99-100, 100-101, 101-102, and 102-103; and

wherein optionally said flt-3 receptor agonist polypeptide is immediately preceded by (methionine⁻¹), (alanine⁻¹) or (methionine⁻², alanine⁻¹).

The examiner relies on the following references:

Gearing et al. (Gearing)	5,420,247	May 30, 1995
Lyman et al. (Lyman)	5,554,512	September 10, 1996
Pastan et al. (Pastan)	5,635,599	June 03, 1997

Chaudhary et al. (Chaudhary), "A recombinant immunotoxin consisting of two antibody variable domains fused to Pseudomonas exotoxin," Nature, Vol. 339, pp. 394-397 (1989)

Hannum et al. (Hannum), "Ligand for FLT3/FLK2 receptor tyrosine kinase regulates growth of haematopoietic stem cells and is encoded by variant RNAs," Nature, Vol. 368, pp. 643-648 (1994)

Claims 1-11 stand rejected under 35 U.S.C. § 103 as obvious over the combined teachings of Pastan, Lyman, Hannum, Chaudhary, and Gearing.

We reverse.

Background

Appellants' specification discloses that the

flt3 ligand is a hematopoietic growth factor which has the property of being able to regulate the growth and differentiation of hematopoietic progenitor and stem cells. Because of its ability to support the growth and proliferation of progenitor cells, flt3 receptor agonists have potential for therapeutic use in treating hematopoietic disorders such as aplastic anemia and myelodysplastic syndromes. Additionally, flt3 receptor agonists will be useful in restoring hematopoietic cells to normal amounts in those cases where the number of cells has been reduced due to diseases or to therapeutic treatments such as radiation and chemotherapy.

Page 2. The specification also discloses flt3 receptor agonists in which the amino acid sequence of the native flt3 ligand is rearranged such that the amino and carboxyl termini of the native sequence are joined to each other (directly or through a linker), and the resulting "circularized" sequence is reopened at another point to create new amino and carboxy termini. See, e.g., page 9.

Discussion

Claim 1 is directed to flt3 receptor agonists comprising at least the first 132 amino acids of SEQ ID NO:144, in which the amino acid sequence is rearranged so that the N-terminus and C-terminus are joined, directly or through a linker, and new N- and C-termini are created in one of thirty-two specific

locations in the rearranged sequence. The examiner rejected claim 1 as obvious in view of Pastan, Lyman, and Hannum.¹ The examiner characterized Pastan as teaching “fusion proteins comprising circularly permuted ligands . . . wherein the amino and carboxy ends are joined together, optionally through a linker, and new amino and carboxy terminal ends are formed at a different location within the ligand.” Examiner’s Answer, page 4. The examiner also cited Pastan as teaching that the disclosed method can be applied to growth factors, and that

preferred opening sites will be located in regions that do not show a highly regular three-dimensional structure. Thus, it is preferred that opening sites be selected in regions of the protein that do not show secondary structure such as alpha helices, pleated sheets, $\alpha\beta$ barrel structure, and the like.

Examiner’s Answer, pages 4-5. The examiner acknowledged that Pastan does not teach or suggest a circularly permuted flt3 ligand. Id., page 5.

The examiner cited Lyman as teaching the flt3 ligand, its usefulness in “peripheral blood progenitor or stem cell transplantation procedures,” and the advantages of soluble flt3 ligand. Examiner’s Answer, page 5. She cited Hannum as disclosing a more detailed structural analysis of the flt3 ligand, including its amino acid sequence (showing that SEQ ID NO:144 terminates prior to the transmembrane domain) and the predicted locations of α helices and β sheets.

¹ The examiner also cited Chaudhary and Gearing in the statement of the rejection. In the explanation of the rejection, however, it is clear that Chaudhary and Gearing are relevant only to the linker sequence that may be used to join the native N- and C-termini. Thus, although Chaudhary and Gearing are relevant to the obviousness of certain dependent claims, they are not required for the prima facie case with respect to claim 1.

The examiner concluded that

[i]t would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the fusion proteins of Pastan et al. . . . by substituting for the cytokines disclosed therein the soluble flt3 ligand disclosed by Lyman et al. One of ordinary skill in the art would have been motivated to make circularly permuted forms of the soluble flt3 ligand disclosed by Lyman et al. by the disclosure of Pastan et al. that such circularly permuted proteins are expected to retain or have improved binding properties to the receptor to which they bind, as compared to the non-permuted forms. The particular termini recited in claim 1 are considered to be obvious in view of Hannum et al., which discloses . . . that such sites occur in regions between alpha helices, given that Pastan et al. teach that regions that do not show a highly regular three-dimensional structure are desirable for introducing the new termini to the circularly permuted protein.

Id., page 6.

Appellants argue that the examiner has not shown prima facie obviousness, because, inter alia, the cited references at best would have made the claimed invention “obvious to try.” See the Appeal Brief, pages 12-17. Appellants argue that the cited references would not have led those of skill in the art to reasonably expect that a circularly permuted flt3 ligand would retain the binding activity of the native ligand, much less have improved binding properties, because the record shows that circular permutation produces unpredictable effects. In support, Appellants refer to the prior art cited in the present specification (pages 3-7), which lists sixteen proteins which have been circularly permuted, and which concludes that

[t]he results of these studies have been highly variable. In many cases substantially lower activity, solubility or thermodynamic stability were observed [listing seven proteins]. . . . In other cases, the sequence rearranged protein appeared to have many nearly identical properties as its natural counterpart [listing eight

proteins]. . . . In exceptional cases, an unexpected improvement over some properties of the natural sequence was observed [listing two proteins].

Specification, page 6. Appellants argue that in view of the prior art as a whole,

one skilled in the art would appreciate that it is an unpredictable [sic] that a circular permuted molecule would have comparable activity of the native ligand. The prior art provides only a very limited number of examples of circular permuted proteins and the results have been variable. . . . In many of these studies, circular permutation disrupted the structure of the protein, and hence the bioactivity. . . . There is no teaching in '599 [Pastan], Hannum or Lyman about whether circular permuteins of flt3 ligand will fold properly and maintain biological activity.

Appeal Brief, page 15.

Prima facie obviousness under 35 U.S.C. § 103 requires that the prior art would have led a person of ordinary skill in the art to make the claimed invention, with a reasonable expectation of success. See, e.g., In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1443 (Fed. Cir. 1991). By contrast, “[a]n ‘obvious-to-try’ situation exists when a general disclosure may pique the scientist’s curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued.” In re Eli Lilly & Co., 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990). “[O]bvious to try’ is not the standard under § 103.” In re O’Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988).

In this case, we agree with Appellants that the cited references may have made it obvious to try making circularly permuted flt3 ligands, but they do not support a prima facie case under § 103. Pastan discloses the concept of

circularly permuting ligands generally. Pastan states that in some ligands, such as interleukin-4, the amino and carboxy termini of the protein are situated relatively close to the active site when the protein is folded into its native conformation. As a result, when fusion proteins are formed by joining a second protein to either the amino or carboxy terminus of such ligands, the resulting fusion may have reduced binding affinity or specificity relative to the native ligand. See column 6, lines 8-18; column 2, lines 5-26. It was this problem that Pastan sought to address by joining the native N- and C-termini and creating new termini by circular permutation. See column 6, lines 19-26.

The prior art relied on by the examiner does not suggest fusing the flt3 ligand to another protein at the N- or C-terminus. Rather, the examiner's rationale for combining the references was that "such circularly permuted proteins are expected to retain or have improved binding properties to the receptor to which they bind, as compared to the non-permuted forms." Examiner's Answer, page 6. The basis for this position is Pastan's statement (column 5, lines 61-64) that "[t]he present invention provides for circularly permuted ligands which possess specificity and binding affinity comparable to or greater than the specificity and binding affinity of the native (unpermuted) ligand."

We do not find that this statement, considered in view of the prior art as a whole, would have provided the requisite motivation or expectation of success. Pastan provides a single example of a successful circularly permuted ligand. See Examples 1 and 2, columns 19-23 (showing that circularly permuted interleukin-4 retained activity, both alone and as a fusion protein with

Pseudomonas exotoxin). Pastan provides additional prophetic examples, but no further evidence to support the position that, for all proteins, circular permutation would be expected to result in “circularly permuted ligands which possess specificity and binding affinity comparable to or greater than the specificity and binding affinity of the native (unpermuted) ligand.”

On the other hand, the present specification provides evidence that the effect of circular permutation is unpredictable. The specification lists sixteen examples of proteins in which circular permutation has been attempted. See pages 4-6. These examples include the IL-4-Pseudomonas exotoxin fusion protein exemplified by Pastan. Page 6, lines 15-18. The specification notes that Pastan’s fusion protein was one of only two examples in which circular permutation resulted in a protein having improved properties compared to the native protein. See page 6, line 32 to page 7, line 2. In the vast majority of cases, the best result that could be expected from circular permutation was that the permuted protein would behave basically the same as the native protein. And, in many cases, “substantially lower activity, solubility or thermodynamic stability were observed.” Specification, page 6, lines 21-22.

While structural similarity is enough, in some cases, to show prima facie obviousness, in such cases, the claimed and known compounds share a similarity of structure that provides an expectation that the compounds will also share similar properties. That is, the structural similarity itself would provide motivation to modify the known compound with a reasonable expectation of producing a similar compound having similar properties. See In re Payne, 606

F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979) (“An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties.”). Here, by contrast, the evidence shows that circular permutation has an unpredictable effect on a ligand’s activity. Thus, even though a circularly permuted ligand has some structural similarity to the native ligand, that similarity does not carry with it an expectation that the two compounds will share similar properties.

Pastan’s disclosure that one circularly permuted ligand has improved properties may have made it obvious to try circularly permuting other ligands, but none of the cited references suggests any reason to circularly permute flt3 ligand specifically. In addition, the prior art as a whole shows that the effect of circular permutation was unpredictable. Thus, the evidence of record does not show that a skilled artisan, with no knowledge of the claimed invention, would select the known circular permutation method and the known flt3 ligand for combination in the manner claimed. Cf. Ecolochem, Inc. v. Southern Calif. Edison Co., 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1075 (Fed. Cir. 2000) (An adequate showing of motivation to combine requires “evidence that ‘a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.’”). The cited references therefore do not support a prima facie case of obviousness.

Summary

The cited references would not have led a person of ordinary skill in the art to make the instantly claimed product with a reasonable expectation of success. We therefore reverse the rejection under 35 U.S.C. § 103.

REVERSED

William F. Smith)	
Administrative Patent Judge)	
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)	BOARD OF PATENT
Demetra J. Mills)	
Administrative Patent Judge)	APPEALS AND
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)	INTERFERENCES
)	
Eric Grimes)	
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