

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

## UNITED STATES PATENT AND TRADEMARK OFFICE

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### BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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Ex parte STEVEN E. BRENNER,  
RICHARD E. GREEN, and  
BENJAMIN P. LEWIS

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Appeal No. 2006-1569  
Application No. 10/159,997

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ON BRIEF

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Before MILLS, GRIMES, and GREEN, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

#### DECISION ON APPEAL

This appeal involves claims to a method of identifying alternatively spliced mRNA products of known genes. The examiner has rejected the claims as directed to non-statutory subject matter, indefinite, anticipated, and obvious. We have jurisdiction under 35 U.S.C. § 134. We reverse all of the rejections.

#### Background

“Although studies have shown that alternative splicing plays a major role in generating protein diversity, standard analyses may not provide a full appreciation of how alternative splicing modulates gene function. Due to the limitations of the ESTs

from which alternative splicing information is commonly derived, researchers often restrict their analyses to the simple splicing modes. . . . A more complete understanding of alternative splicing requires an unbiased consideration of all alternative mRNA isoforms.” Specification, page 1.

The specification discloses “a protocol to systematically identify alternative mRNA isoforms of known human genes.” Page 3. The specification describes “an exemplary implementation of this protocol” as follows:

[W]e map mRNAs from the RefSeq database to contig sequences from the NCBI human genome, requiring that an mRNA align to genomic sequence over the full length of the coding sequence, without gaps in the exons. We further require 98% identity between the sequences, favoring RefSeq sequence in case of nucleotide mismatch. When multiple RefSeq mRNAs align to the same region of genomic sequence, we use only the mRNA containing the largest number of exons.

Page 4. This part of the protocol “identif[ies] target gene sequences.” Page 3, lines 13-21. The subsequent steps are described as follows:

To detect alternate isoforms, we align EST sequences from dbEST to the genomic sequence and use TAP [transcript assembly protocol; specification, page 4, line 7] to infer alternate mRNA splice forms from these alignments. Since we use known genes, the reading frame of the primary mRNA isoforms (i.e., the RefSeq mRNAs) is known. So that the reading frame can be determined for all EST-suggested alternate isoforms, we restrict our set to cases in which the 5' end of the EST sequences align to coding sequences of the RefSeq mRNA. We also exclude cases of intron retention, as these are indistinguishable from incompletely-processed transcripts, a common dbEST contaminant. We have higher confidence in splicing events with coverage by multiple ESTs.

Page 4.

## Discussion

### 1. Claim construction

Claims 1-4 are pending and on appeal. Claim 1 is the only independent claim and reads as follows:

1. A computational method for systematically identifying alternative mRNA splice isoforms of known genes, the method comprising the steps of:
  - a) identifying target gene sequences by mapping mRNA sequences of an mRNA sequence dataset to genomic sequences of a genomic DNA sequence dataset, wherein:

each mRNA sequence is required to align to a corresponding genomic sequence over the full length of the coding sequence of the mRNA sequence, without gaps in the exons of the genomic sequence; and

at least 98% identity between each mRNA sequence and the corresponding genomic sequence is required, favoring the mRNA sequence in case of nucleotide mismatch; and

b) identifying a dataset of alternate mRNA splice isoforms of the target gene sequences by aligning EST sequences from an EST sequence dataset to the target gene sequences and using a transcript assembly protocol, wherein:

the alternative mRNA splice isoform dataset is restricted to mRNA sequences in which the 5' end of an EST sequence aligns to a coding sequence of the corresponding mRNA sequence, such that the reading frame of the coding sequences can be determined for all isoforms of the dataset, and

isoforms presenting intron retention are excluded from the alternative mRNA splice isoform dataset, and

coverage by multiple EST sequences is required for each splicing event.

Thus, claim 1 is directed to the exemplary embodiment of the disclosed protocol discussed on pages 3-4 of the specification, with the exception that claim 1 is not limited to use of the RefSeq and dbEST databases.

## 2. Definiteness

The examiner rejected claims 1-4 under 35 U.S.C. § 112, second paragraph, as indefinite. The examiner reasoned that “[i]t is unclear whether ‘the dataset’ in line 16 [of claim 1; lines 19-20 as reproduced above] is directed to the mRNA sequence dataset (lines 3-4 [line 4 above]), or alternate mRNA splice isoform dataset (line 10 [line 12 above]). Claims 2-4 are rejected for being dependent from claim 1.” Examiner’s Answer, page 7.

Appellants argue that “[t]he objected-to ‘dataset’ of claim 1 must be read in its context – it is contained in the phrase: ‘the alternate mRNA splice isoform dataset is restricted to mRNA sequences in which the 5’ end of an EST sequence aligns to a coding sequence of the corresponding mRNA sequence, such that the reading frame of the coding sequences can be determined for all isoforms of the dataset.’ In this context, there is no doubt that ‘the dataset’ refers to the immediately antecedent ‘alternative mRNA splice isoform dataset.’” Appeal Brief, page 5.

We agree with Appellants’ position. The context of the claim makes it reasonably clear that the phrase “all isoforms of the dataset” refers to the isoforms in the “alternative mRNA splice isoform dataset.” Claims are in compliance with 35 U.S.C. § 112, second paragraph, if “the claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits.”

Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94-95 (Fed. Cir. 1987). That standard is met here. The rejection for indefiniteness is reversed.

### 3. Anticipation

The examiner rejected claim 1 under 35 U.S.C. § 102(a) as anticipated by Honkura.<sup>1</sup> The examiner reasoned that

Honkura et al. discloses a computer method for identifying alternative mRNA splice isoforms of known genes via the Gene Resource Locator (GRL) to assemble gene maps (Abstract, etc.). Honkura et al. aligns full-length enriched cDNA sequences with authentic 5'-terminal start points for identification [of] promoter regions (page 222, column 2, last paragraph). . . . The method of Honkura et al. involves the alignment of ESTs from various sources, such as UniGene and full-length cDNA databases (mRNA sequences).

Examiner's Answer, pages 8-9.

Appellants argue that Honkura's method does not meet all the limitations of the instant claims: "Honkura includes no step comparable to our first step: identifying target gene sequences by mapping mRNA sequences of an mRNA sequence data set to genomic sequence. In contrast, Honkura directly aligns ESTs of Unigene [database] with genomic sequence. . . . The inputs to Honkura's analysis pipeline are EST sequences and genomic sequence. . . . The initial inputs to our protocol are the well-characterized RefSeq genes [i.e., mRNAs] whose coding regions are known and genomic sequence. In a later step, ESTs are aligned to the RefSeq loci to reveal patterns of alternate splicing." Appeal Brief, page 9.

The standard for anticipation is one of strict identity. See Verdegaal Bros., Inc. v. Union Oil Co., 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) ("A claim is

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<sup>1</sup> Honkura et al., "The Gene Resource Locator: gene locus maps for transcriptome analysis," Nucleic Acids Research, Vol. 30, pp. 221-225 (2002)

anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.”). In this case, we agree with Appellants that the method disclosed by Honkura does not meet all the limitations of the instant claims.

As Appellants have pointed out, the instant claims require a first step of “mapping mRNA sequences of an mRNA sequence dataset to genomic sequences of a genomic DNA sequence dataset.” The examiner has pointed to no disclosure in Honkura of a step of comparing the sequences in an mRNA sequence dataset to the sequences in a genomic DNA sequence dataset, and no such disclosure is apparent to us.

We do not find persuasive the examiner’s argument that steps (a) and (b) of the claimed method are anticipated because they are akin to product-by-process claims. See the Examiner’s Answer, pages 9-10. Instant claim 1 is directed to a process, not a product. Therefore, it is not anticipated by a different process that was known in the art, even if the known process produced the same end product.

The rejection of claim 1 as anticipated by Honkura is reversed.

#### 4. Obviousness

The examiner rejected claims 1-4 under 35 U.S.C. § 103 as obvious in view of Honkura and Sun.<sup>2</sup> The examiner relied on Honkura as teaching the basic method of claim 1 and cited Sun for teaching limitations related to cancer cells and nonsense-mediated decay (recited in claims 2-4).

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<sup>2</sup> Sun et al., “Nonsense-mediated decay of glutathione peroxidase 1 mRNA in the cytoplasm depends on intron position,” The EMBO Journal, Vol. 19, pp. 4734-4744 (2000)

We have already found, however, that Honkura does not disclose a method meeting all the limitations of claim 1. The examiner has pointed to nothing in Sun that would remedy the deficiencies discussed above. We reverse the rejection under 35 U.S.C. § 103 because the examiner has not adequately explained how the combined references teach or would have suggested a method meeting all the limitations of the instant claims.

#### 5. Statutory subject matter

The examiner rejected claims 1-4 under 35 U.S.C. § 101 “because the claimed invention is directed to non-statutory algorithm type subject matter.” Examiner’s Answer, page 3. The examiner reasoned that the

claims are directed to a computer method comprising processes performed within a computer system without resulting in any physical transformations outside of said computer. A method wherein the transformation of signals or data inside a computer without a means for transforming said data to produce a useful, concrete, and tangible result is regarded as being non-statutory. (MPEP § 2106 (IV)(B)(2)(b)).

Id.

We will reverse this rejection. The examiner appears to rely on a bright-line rule that a computer-based method must result in a physical transformation outside the computer in order to be considered to produce a useful, concrete, and tangible result and thereby satisfy 35 U.S.C. § 101. The examiner cites the Manual of Patent Examining Procedure § 2106(IV)(B)(2)(b) as the source of this perceived rule. That section of the MPEP does not support the rule the examiner appears to rely on. It states that “[t]o be statutory, a claimed computer-related process must either: (A) result

in a physical transformation outside the computer . . . or (B) be limited to a practical application within the technological arts" (emphasis added).

With regard to the latter, the MPEP states that a "process that merely manipulates an abstract idea or performs a purely mathematical algorithm" is nonetheless statutory if "the claimed process [is] limited to a practical application of the abstract idea or mathematical algorithm in the technological arts. . . . A claim is limited to a practical application when the method, as claimed, produces a concrete, tangible and useful result; i.e., the method recites a step or act of producing something that is concrete, tangible and useful." MPEP § 2106(IV)(B)(2)(b)(ii).

In addition, we note that the section of the MPEP on which the examiner relies has been superseded by the Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility, 1300 Off. Gaz. Pat. Office 142 (November 22, 2005) (accessible on-line at [www.uspto.gov/go/og/2005/week47/patgupa.htm](http://www.uspto.gov/go/og/2005/week47/patgupa.htm)). The Interim Guidelines expressly state that "physical transformation 'is not an invariable requirement, but merely one example of how a mathematical algorithm [or law of nature] may bring about a useful application.'" Id. at 146<sup>3</sup> (quoting AT&T Corp. v. Excel Commc'ns, Inc., 172 F.3d 1352, 50 USPQ2d 1447 (Fed. Cir. 1999), alteration in original). The Interim Guidelines state that a process that does not result in physical transformation may nonetheless be statutory if it achieves a useful, concrete and tangible result. Id.

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<sup>33</sup> Page 20 of the on-line version of the Interim Guidelines.

The Interim Guidelines also defines the terms “useful”, “concrete” and “tangible” as they are to be applied during examination. See id. We note that the terms “tangible” and “concrete” do not require physical transformation of objects outside the computer. See id. (“The tangible requirement does not necessarily mean that a claim . . . must operate to change articles or materials to a different state or thing”)<sup>4</sup> and (to “produce[ ] a ‘concrete’ result . . . the process must have a result that can be substantially repeatable or the process must substantially produce the same result again.”).<sup>5</sup>

The Interim Guidelines, in analyzing the relevant case law, provide the following guidance for determining whether a claimed process is statutory: “The focus of the inquiry is on whether the claim, considered as a whole, constitutes ‘a practical application of an abstract idea.’ . . . [A]n ‘abstract idea’ when practically applied to a useful end is eligible for a patent.” Id. at 149.<sup>6</sup> In addition, “[t]he focus is not on whether the steps taken to achieve a particular result are useful, tangible and concrete, but rather that the final result is ‘useful, tangible and concrete.’” Id.<sup>7</sup>

Here, the result of the claimed process is a dataset of alternate mRNA splice isoforms of the target gene sequences. The specification states that this dataset is useful “for identifying which isoforms of a gene will be expressed” (page 6, line 6), for engineering genes to predictively undergo alternative splicing and thereby control gene expression (page 6, last paragraph), and for “generating transgenic animals in which

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<sup>4</sup> Page 21 of the on-line version of the Interim Guidelines.

<sup>5</sup> Page 21 of the on-line version of the Interim Guidelines.

<sup>6</sup> Page 37 of the on-line version of the Interim Guidelines.

<sup>7</sup> Page 38 of the on-line version of the Interim Guidelines.

expression of exogenous genetic material is limited to certain cell types based on their splicing environment.” Page 7, lines 6-8.

The examiner has not adequately explained why the claimed process does not produce a result that is useful, tangible, and concrete, as those terms are defined in the Interim Guidelines. Because the examiner has the initial burden of showing unpatentability, see In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995), and that burden has not been carried here, we reverse the rejection of claims 1-4 under 35 U.S.C. § 101.

Summary

The examiner has not adequately shown that the claims are unpatentable for indefiniteness, anticipation, or obviousness, or that they are directed to non-statutory subject matter. The rejections on appeal are reversed.

REVERSED

Demetra J. Mills	)
Administrative Patent Judge	)
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	)
	) BOARD OF PATENT
Eric Grimes	)
Administrative Patent Judge	) APPEALS AND
	)
	) INTERFERENCES
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Lora M. Green	)
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