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90/009,017	03/17/2008	6881571	37087-8012	5593

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101 FEDERAL STREET  
BOSTON, MA 02110

EXAMINER

ART UNIT            PAPER NUMBER

DATE MAILED: 05/01/2008

Please find below and/or attached an Office communication concerning this application or proceeding.



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(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

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CENTRAL REEXAMINATION UNIT

## **EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM**

REEXAMINATION CONTROL NO. 90/009,017.

PATENT NO. 6881571.

ART UNIT 3991.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

<b>Order Granting / Denying Request For Ex Parte Reexamination</b>	<b>Control No.</b> 90/009,017	<b>Patent Under Reexamination</b> 6881571	
	<b>Examiner</b> Padmashri Ponnaluri	<b>Art Unit</b> 3991	

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--**

The request for *ex parte* reexamination filed 17 March 2008 has been considered and a determination has been made. An identification of the claims, the references relied upon, and the rationale supporting the determination are attached.

Attachments: a)  PTO-892,      b)  PTO/SB/08,      c)  Other: \_\_\_\_\_

1.  The request for *ex parte* reexamination is GRANTED.

**RESPONSE TIMES ARE SET AS FOLLOWS:**

For Patent Owner's Statement (Optional): **TWO MONTHS** from the mailing date of this communication (37 CFR 1.530 (b)). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).**


For Requester's Reply (optional): **TWO MONTHS** from the **date of service** of any timely filed Patent Owner's Statement (37 CFR 1.535). **NO EXTENSION OF THIS TIME PERIOD IS PERMITTED.** If Patent Owner does not file a timely statement under 37 CFR 1.530(b), then no reply by requester is permitted.

2.  The request for *ex parte* reexamination is DENIED.

This decision is not appealable (35 U.S.C. 303(c)). Requester may seek review by petition to the Commissioner under 37 CFR 1.181 within **ONE MONTH** from the mailing date of this communication (37 CFR 1.515(c)). **EXTENSION OF TIME TO FILE SUCH A PETITION UNDER 37 CFR 1.181 ARE AVAILABLE ONLY BY PETITION TO SUSPEND OR WAIVE THE REGULATIONS UNDER 37 CFR 1.183.**

In due course, a refund under 37 CFR 1.26 ( c ) will be made to requester:

- a)  by Treasury check or,  
b)  by credit to Deposit Account No. \_\_\_\_\_, or  
c)  by credit to a credit card account, unless otherwise notified (35 U.S.C. 303(c)).

  
Padmashri Ponnaluri  
Primary Examiner  
Art Unit: 3991

cc:Requester ( if third party requester )

***DETAILED ACTION: Reexamination: Granting of Request***

***Procedural Posture:***

The Third Party Request (filed on 3/17/08) for *ex parte* reexamination of claims 1-22 of United States Patent Number 6,881,571 B1 (Schweighoffer et al) is acknowledged, and reexamination control number 90/009,017 is assigned.

***Decision Granting the Order***

A substantial new question of patentability affecting **claims 1-22** of United States Patent Number 6,881,571 B1 (Schweighoffer et al) is raised by the request for reexamination.

***Status of Claims***

Claims 1-22 are present in the '571 patent.

Claims 1-22 are currently subject to reexamination proceedings.

***Information Disclosure Statement***

The Information disclosure statement (PTO/SB/08) filed on 3/17/08 has been considered.

***Priority***

The current '571 patent is issued from application 09/623,828, filed on March 11, 1999;

Which is a Continuation-in-Part of application 09/046,920, filed on March 24, 1998, now US Patent 6,251,590.

The 09/046,920 specification discloses method of identifying within a biological sample, alternatively spliced nucleic acid regions occurring between two physiological conditions. The 09/046,920 specification does not disclose "device for identifying at least one differentially spliced gene product" and "second oligonucleotide molecule comprises a second sequence that is

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complementary to and specific for an exon-exon or exon-intron junction region of said first gene.”

Thus the present claims 1-22 are entitled to the priority date of the present 09/623,828 application, which has a filing date of March 11, 1999 for prior art purposes.

### ***Ongoing Duty to Disclose***

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 6,881,571 throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286. The third party requester is also reminded of the ability to similarly appraise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

### ***Substantial New Question of Patentability (SNQ) Raised By the Request***

For “a substantial new question of patentability” to be present, it is only necessary that:

A. The prior art patents and/or printed publications raise a substantial question of patentability regarding at least one claim i.e. the prior art teaching is such that there is a substantial likelihood that a reasonable examiner would consider the teaching to be important in deciding whether or not the claim is patentable; and it is not necessary that the prior art establish a prima facie case of unpatentability and;

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B. The same question of patentability as to the claim has not been decided by the Office in a previous examination or pending reexamination of the patent or in a final holding of invalidity by the Federal Courts in a decision on the merits involving the claim. See MPEP 2242.

For a reexamination that was ordered on or after November 2, 2002 (the date of enactment of Public Law 107-273; see Section 13105, of the Patent and Trademark Office Authorization Act of 2002), reliance *solely* on old art (as the basis for a rejection) does not necessarily preclude the existence of a substantial new question of patentability (SNQ) that is based exclusively on that old art. Determinations on whether a SNQ exists in such an instance shall be based upon a fact-specific inquiry done on a case-by-case basis. For example, a SNQ may be based solely on old art where the old art is being presented/viewed in a new light, or in a different way, as compared with its use in the earlier concluded examination(s), in view of a material new argument or interpretation presented in the request. MPEP 2258.01.

#### ***Scope of Reexamination***

The reexamination proceeding provides a complete reexamination of the patent claims on the basis of prior art patents and printed publications. 37 CFR 1.552, MPEP 2258.

The third party requester discussion that “the current patent claims are not supported by an adequate written description or enabling disclosure as required by 35 USC 112. first paragraph” (see the request page 36) is outside the scope of reexamination and thus has no bearing on the raising of SNQ.

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In the '571 patent 22 claims are present, of which independent claim 1 is drawn to a device and independent claim 12 is drawn to a method of producing the device.

The independent claims 1 and 12 are appended below.

**Claim 1.** A device for identifying at least one differentially spliced gene product, wherein said device comprises a solid support material and single-stranded oligonucleotides of between 5 and 100 nucleotides in length attached to said support material, wherein said oligonucleotides comprise at least a first and a second oligonucleotide molecule arranged serially on the support material, wherein said first oligonucleotide molecule comprises a first sequence that is complementary to and specific for an exon or an intron of a first gene, and wherein said first sequence corresponds to a region of variability in at least one product of said first gene due to differential splicing, and wherein said second oligonucleotide molecule comprises a second sequence that is complementary to and specific for an exon-exon or exon-intron junction region of said first gene, and wherein said second sequence corresponds to a region of variability in at least one product of said first gene due to differential splicing, said device allowing, when contacted with a sample containing at least one nucleic acid molecule under conditions allowing hybridization to occur, the determination of the presence or absence of said differentially spliced gene product.

**Claim 12.** A method of producing a device comprising a support material and single-stranded oligonucleotide of between 5 and 100 nucleotides in length attached to said solid support material, wherein said method comprises:

(a) providing said oligonucleotides, wherein said oligonucleotides comprise at least a first and a second oligonucleotide molecule, wherein said first oligonucleotide molecule comprises a first sequence that is complementary to and specific for an exon or an intron of a first gene, and wherein said first sequence corresponds to a region of variability in at least one product of said first gene due to differential splicing, and wherein said second oligonucleotide molecule comprises a second sequence that is complementary to and specific for an exon-exon or exon-intron junction region of said first gene, and wherein said second sequence corresponds to a region of variability in at least one product of said first gene due to differential splicing; and

(b) arranging and immobilizing said oligonucleotides serially on said support material, said device allowing, when contacted with a sample containing at least one nucleic acid molecule under conditions allowing hybridization to occur, the determination of the presence or absence of at least one differentially spliced gene product.

*Documents cited by the Requester*

1. Kusiak and Norton (1993) Molec. Brain. Res. 20:64-70 (Kusiak et al).

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2. Virts et al. (1998) *Molecular Immunology* 35:167-76.
3. WO 95/27052 (Publication date 10/12/1995).
4. Wang et al. (1995) *Biochimica et Biophysica Acta* 1271:358-62.
5. U.S. Pat. No. 5,057,410 (Kawasaki et al, issued on 10/15/1991).
6. Chee et al. (US. Patent No. 5,837,832, issued on 11/17/1998).
7. Alnemri, E.S. et al. (1995) *J. Biol. Chem.* 270:4312-17.
8. Hillman et al (US Patent 6,168,920, issued on 1/2/2001, filing date August 10, 1998).
9. Gelfand et al. (January 1999) *Nucleic Acids Res.* 27. No. 1, pages 301-02.

The above listed documents 1-5, 7-9 were neither cited nor used in rejections during the prosecution of the application that resulted in the present '571 patent.

Chee et al was used in combination with US Patent 6,251,590 in obviousness-type-double patenting rejection (see 3/25/03 FAOM) in the application 09/623,828 that resulted into the current '571 patent. In this reexamination proceedings, Chee et al is used in a combination with other references which were never used in the application that resulted in the current patent.

#### *Discussion of the Cited Documents*

1. Kusiak et al (Kusiak and Norton (1993) *Molec. Brain. Res.* 20:64-70) ) raises a substantial new question of patentability of claims of the present US Patent 6,881,571(Schweighoffer et al) (see the request filed 3/17/08, pages 5-10, 29-35). Kusiak et al was neither cited nor used in rejecting the present claims during the prosecution of the application that resulted in the present '571 patent.

Kusiak discloses a Northern blot method and blot (support) that includes an exon probe and a splice junction probe for distinguishing different splice variants (see pages 66- 67). The probes are about 30 nucleotides in length (see page 65). Kusiak discloses that the probes (oligonucleotides) are arranged in a serial or adjacent arrangement (see figures 3 and 4). Kusiak teaches that the insert probe hybridizes to an exon sequence present only in transcripts lacking a deleted exon (see abstract). The "splice junction" probe hybridizes to an exon-exon junction sequence present only in transcripts including both exons, which represents "a region of

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variability" (see Kusiak Abstract; Figures 3 and 4). The described Northern blot device is used to determine the presence or absence of differentially spliced gene product (see Kusiak page 66).

There is a substantial likelihood that a reasonable examiner would consider the teachings of Kusiak important in deciding the patentability of claims 1-22 of the present US Patent 6,881,571.

2. Virts et al ( (1998) Molecular Immunology 35:167-76) raises a substantial new question of patentability of claims of the present US Patent 6,881,571(Schweighoffer et al) (see the request filed 3/17/08, pages 10-14, 29-35). Virts et al was neither cited nor used in rejecting the present claims during the prosecution of the application that resulted in the present '571 patent.

Virts et al discloses a Southern blot method and blot (support) using exon and exon-exon junction probes to distinguish splice variants (see Fig. 1 page 170; Fig. 2, page 171; Fig. 6, page 174). The probes are about 30 nucleotides in length (see Virts et al Table 2, page 169).

There is a substantial likelihood that a reasonable examiner would consider the teachings of Virts et al important in deciding the patentability of claims 1-22 of the present US Patent 6,881,571.

3. WO 95/27052 (Publication date 10/12/1995) raises a substantial new question of patentability of claims of the present US Patent 6,881,571(Schweighoffer et al) (see the request filed 3/17/08, pages 14-19, 29-35). WO 95/27052 was neither cited nor used in rejecting the present claims during the prosecution of the application that resulted in the present '571 patent.

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WO 95/27052 discloses novel splice mutants of interleukins-2 and 4, which contain exons 1, 3 and 4 of the full-length mRNAs, but have exon 2 deleted. The proteins resulting from the expression of these splice mutants are useful in regulating the activity of the full-length interleukins (see WO 95/27052 abstract). WO 95/27052 discloses a Southern blot method that includes exon-exon junction probes for distinguishing different splice variants (see page 17).

There is a substantial likelihood that a reasonable examiner would consider the teachings of WO 95/27052 important in deciding the patentability of claims 1-22 of the present US Patent 6,881,571.

4. Wang et al ((1995) *Biochimica et Biophysical Acta* 1271:358-62) raises a substantial new question of patentability of claims of the present US Patent 6,881,571 (Schweighoffer et al) (see the request filed 3/17/08, pages 19-23, 29-35). Wang et al was neither cited nor used in rejecting the present claims during the prosecution of the application that resulted in the present '571 patent.

Wang et al disclose a dot blot using exon or exon-exon junction probes for distinguishing splice variants (see page 359, column 2 and page 361, column 1). The probes are about 25-30 nucleotides in length (see Table 1, page 359).

There is a substantial likelihood that a reasonable examiner would consider the teachings of Wang et al important in deciding the patentability of claims 1-22 of the present US Patent 6,881,571.

5. Kawasaki et al (US Patent 5,057,410, issued on 10/15/1991) raises a substantial new question of patentability of claims of the present US Patent 6,881,571 (Schweighoffer et al) (see

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the request filed 3/17/08, pages 23-35). Kawasaki et al was neither cited nor used in rejecting the present claims during the prosecution of the application that resulted in the present '571 patent.

Kawasaki et al discloses methods for detecting chimeric RNAs using, for example, probes specific for exon-exon junctions (see column 4, lines 44-50; column 8, lines 64-68; column 11, lines 5-10; column 14, lines 29-32; column 15, lines 32-34; claim 16; and claim 19). The data may be presented in the form of an autoradiograph of a Southern blot (see column 5, lines 13-34). The probes are about 25-30 nucleotides in length.

There is a substantial likelihood that a reasonable examiner would consider the teachings of Kawasaki et al important in deciding the patentability of claims 1-22 of the present US Patent 6,881,571.

6. Chee et al (US. Patent No. 5,837,832, issued on 11/17/1998) raises a substantial new question of patentability of claims of the present US Patent 6,881,571 (Schweighoffer et al) (see the request filed 3/17/08, pages 29-35).

Chee et al discloses arrays of oligonucleotide probes immobilized on a solid support (see column 1, line 58- column 2, line 48; claim 1), including exon probes (see column 9, lines 32-38; column 10, lines 26-39; and claim 11). Chee et al teach that the exon arrays, which can be used to detect the presence or absence of exons in splice variants.

It is agreed that consideration of Chee in combination with Kusiak, Virts, Wang and Kawasaki references raises a substantial new question of patentability as to the instant claims that has not been decided during the prosecution of the application that resulted into the current patent. Chee et al is being used in a new light as asserted by the Requester on pages 29-35 of the request. There is a substantial likelihood that a reasonable examiner would consider the teachings

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of Chee et al important in deciding the patentability of claims 1-22 of the present US Patent 6,881,571.

7. Alnemri, E.S. et al. ((1995) J. Biol. Chem. 270:4312-17) raises a substantial new question of patentability of claims of the present US Patent 6,881,571 (Schweighoffer et al) (see the request filed 3/17/08, pages 29-35). Alnemri et al was neither cited nor used in rejecting the present claims during the prosecution of the application that resulted in the present '571 patent.

Alnemri et al teaches that alternative splicing contributes to different apoptotic activities in the gene products of *bclx* and *grb2* genes (see Alnemri page 4317).

There is a substantial likelihood that a reasonable examiner would consider the teachings of Alnemri et al important in deciding the patentability of claims 1-22 of the present US Patent 6,881,571.

8. Hillman et al (US Patent 6,168,920, issued on 1/2/2001, filed on August 10, 1998) raises a substantial new question of patentability of claims of the present US Patent 6,881,571 (Schweighoffer et al) (see the request filed 3/17/08, pages 29-35). Hillman et al was neither cited nor used in rejecting the present claims during the prosecution of the application that resulted in the present '571 patent.

Hillman discloses human extracellular adhesive proteins (EXADH) and polynucleotides which identify and encode EXADH (see Hillman abstract). Hillman teaches oligonucleotide fragments derived from any of the polynucleotide sequences described may be used as targets in a micro array. The micro array can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This

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information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents (see Hillman column 30).

There is a substantial likelihood that a reasonable examiner would consider the teachings of Hillman et al important in deciding the patentability of claims 1-22 of the present US Patent 6,881,571.

9. Gelfand et al (Nucleic Acids Res. January 1999. vol. 27, no. 1. pages 301-02) raises a substantial new question of patentability of claims of the present US Patent 6,881,571 (Schweighoffer et al) (see the request filed 3/17/08, pages 29-35). Gelfand et al was neither cited nor used in rejecting the present claims during the prosecution of the application that resulted in the present '571 patent.

Gelfand discloses a data base of Alternatively Spliced genes (ASDB) (see the abstract). ASDB incorporates information about alternatively spliced genes, their products and expression patterns. It can be searched in order to find all products of alternative splicing produced in a particular tissue or a given organism, or all variants generated by a particular transcript. ASDB currently contains about 1700 protein sequences (see Gelfand abstract).

There is a substantial likelihood that a reasonable examiner would consider the teachings of Gelfand et al important in deciding the patentability of claims 1-22 of the present US Patent 6,881,571.

### ***Conclusion***

In view of the above, the request for reexamination is **GRANTED**.

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**Claims 1-22** of United States Patent Number 6,881,571 will be reexamined.

**Extensions of Time**

Extensions of time under 37 CFR 1.136 (a) will not be permitted in these proceedings because the provisions of 37 CFR 1.136 apply only to an applicant and not to parties in a reexamination proceeding. Additionally, 35 U.S.C. 305 requires that ex parte reexamination proceedings “will be concluded with special dispatch” (37 CFR 1.555(a) ). Extensions of time in ex parte reexamination proceedings are provided for in 37 CFR 1.550(c).

**Patent Owner Amendment**

Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37 CFR 1.20(c).

***NOTICE RE PATENT OWNER'S CORRESPONDENCE ADDRESS***

Effective May 16, 2007, 37 CFR 1.33(c) has been revised to provide that:

The patent owner's correspondence address for all communications in an *ex parte* reexamination or an *inter partes* reexamination is designated as the correspondence address of the patent.

*Revisions and Technical Corrections Affecting Requirements for Ex Parte and Inter Partes Reexamination, 72 FR 18892 (April 16, 2007) (Final Rule)*

**The correspondence address for any pending reexamination proceeding not having the same correspondence address as that of the patent is, by way of this revision to 37 CFR 1.33(c), automatically changed to that of the patent file as of the effective date.**

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This change is effective for any reexamination proceeding which is pending before the Office as of May 16, 2007, including the present reexamination proceeding, and to any reexamination proceeding which is filed after that date.

Parties are to take this change into account when filing papers, and direct communications accordingly.

In the event the patent owner's correspondence address listed in the papers (record) for the present proceeding is different from the correspondence address of the patent, it is strongly encouraged that the patent owner affirmatively file a Notification of Change of Correspondence Address in the reexamination proceeding and/or the patent (depending on which address patent owner desires), to conform the address of the proceeding with that of the patent and to clarify the record as to which address should be used for correspondence.

**Telephone Numbers for reexamination inquiries:**

Reexamination and Amendment Practice	(571) 272-7703
Central Reexam Unit (CRU)	(571) 272-7705
Reexamination Facsimile Transmission No.	(571) 273-9900

**Future Correspondences**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padmashri Ponnaluri whose telephone number is 571-272-0809.

The examiner can normally be reached on Monday through Friday between 7 AM and 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Deborah Jones can be reached on 571-272-1535. The fax phone number for the organization where this application or proceeding is assigned is 571-273-9900.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

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applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

All correspondence relating to this Ex parte Reexamination proceeding should be directed to:

By Mail to:

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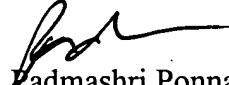
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