METHODS AND COMPOSITIONS IN TREATING PAIN USING DIACYLGLYCEROL KINASE EPSILON
# INTERNATIONAL SEARCH REPORT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>BAJALIEH et al SV2, a Brain Synaptic Vesicle Protein Homologous to Bacterial Transporters, Science, 28 August 1992, Vol. 257, 1271-1273.</td>
<td>1, 2, and 4</td>
</tr>
<tr>
<td>Y</td>
<td>US 5,976,875 A (PRESCOTT et al.) 02 November 1999 (02.11.1999), column 2, lines 13-43 and SEQ ID NO: 1.</td>
<td>1, 2, and 4</td>
</tr>
<tr>
<td>Y</td>
<td>US 6,255,095 B1 (PRESCOTT et al.) 03 July 2001 (03.07.2001), column 2, lines 54-48; column 3, lines 49-53.</td>
<td>1, 2, and 4</td>
</tr>
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</table>

Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search: 03 September 2003 (03.09.2003)

Name and mailing address of the ISA/US:
- Mail Stop PCT, Attn: ISA/US
- Commissioner for Patents
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Date of mailing of the international search report: 09.07.2003

Form PCT/ISA/210 (second sheet) (July 1998)
INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found un searchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos. 1, 2, and 4 drawn to SEQ ID NO: 1

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)
BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to be a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Groups 1-32, claims 1, 2, and 4, in part, drawn, respectively, to methods of identifying compounds capable of treating pain disorders comprising assaying the ability of the compound to modulate the nucleic acid expression of, respectively, 9949 (Group 1), 14230 (Group 2), 760 (Group 3), 6255 (Group 4), 12216 (Group 5), 17719 (Group 6), 41897 (Group 7), 47171 (Group 8), 33408 (Group 9), 10002 (Group 10), 16209 (Group 11), 314 (Group 12), 686 (Group 13), 27410 (Group 14), 33260 (Group 15), 619 (Group 16), 15985 (Group 17), 69112 (Group 18), 2158 (Group 19), 224 (Group 20), 615 (Group 21), 44373 (Group 22), 95431 (Group 23), 22245 (Group 24), 2387 (Group 25), 16558 (Group 26), 55054 (Group 27), 16314 (Group 28), 1613 (Gen p 29), 1675 (Group 30), 9569 (Group 31), and 15424 (Group 32).

Groups 33-64, claims 1, 2, and 4, in part, drawn, respectively, to methods of identifying compounds capable of treating pain disorders comprising assaying the ability of the compound to modulate the polypeptide activity of 9949 (Group 33), 14230 (Group 34), 760 (Group 35), etc.

Groups 65-96, claims 3 and 5-8, in part, respectively, drawn to methods for modulating a pain signaling mechanism in a cell comprising contacting a cell with a nucleic acid expression modulator of 9949 (Group 65), 14230 (Group 66), 760 (Group 67), etc.

Groups 97-128, claims 3 and 5-8, in part, respectively, drawn to methods for modulating a pain signaling mechanism in a cell comprising contacting a cell with a polypeptide activity modulator of 9949 (Group 97), 14230 (Group 98), 760 (Group 99), etc.

Groups 129-160, claims 9-13, in part, respectively, drawn to methods of treating subjects having pain disorders comprising administering to the subject a nucleic acid modulator of 9949 (Group 129), 14230 (Group 130), 760 (Group 131), etc.

Groups 161-192, claims 9-13, in part, respectively, drawn to methods of treating subjects having pain disorders comprising administering to the subject a polypeptide activity modulator of 9949 (Group 161), 14230 (Group 162), 760 (Group 163), etc.

The inventions listed as Groups 1-192 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Claim 1 broadly encompasses the nucleic acid sequences and amino acid sequences of 32 different genes. The nucleic acid molecules of Groups 1-32 are composed of different nucleic acids and are structurally and functionally unrelated, and to each other. Further, locus/accession number U49979 (30 May 1996) teaches the nucleic acid molecule in Group 1 comprised of the nucleic acid sequence of SEQ ID NO: 1. Thus, the technical feature of claim 1 is not a contribution over the prior art and is not considered a special technical feature. Accordingly, each of the 32 different polynucleotide sequences recited in claim 1 are thus not linked under PCT Rule 13.1 and are thus placed in 32 different inventive Groups numbered 1-32, respectively.

The nucleic acid sequence imparts structural and functional differences of each gene which affect properties such as expression levels, tissue specific expression patterns, mRNA half lives, cellular localization of the gene product, etc. Furthermore, each gene encodes a different protein product which is not sufficiently linked by structural or functional features. Additionally, the claimed methods produce different products and/or different results which are not coregressive. Due to the different structural and function imparted upon each nucleic acid molecule by its nucleic acid sequence, it is not expected that the compound of Group 1 would modulate the expression of the nucleic acid molecules of Groups 2-32. In addition, due to the different structure and function imparted upon each polypeptide by its amino acid sequence, it is not expected that the compound of Group 33 would modulate the polypeptide activity of the polypeptides.
of Groups 34-64. Also, unity of invention is lacking for Groups 65-192 because the PCT rules do not provide for the search and examination of more than one method of use and one method of making for the first claimed product.

Groups 2-32 recite the technical feature of identifying a compound capable of treating a pain disorder by assaying the ability of the compound to modulate the expression of a nucleic acid sequence which is not required by the other methods of Groups 1; 33-64.

Groups 33-64 recite the technical feature of identifying a compound capable of treating a pain disorder by assaying the ability of the compound to modulate the polypeptide activity of a polypeptide which is not required by the other methods of Groups 1-32.

Groups 65-96 recite the technical feature of modulating a pain signaling mechanism in a cell comprising contacting a cell with a modulator of nucleic acid expression which is not required by the other methods of Groups 97-128.

Groups 97-128 recite the technical feature of modulating a pain signaling mechanism in a cell comprising contacting a cell with a modulator of polypeptide activity which is not required by the other methods of Groups 65-96.

Groups 129-160 recite the technical feature of treating a subject having a pain disorder comprising administering to the subject a modulator of nucleic acid expression which is not required by the other methods of Groups 161-192.

Groups 161-192 recite the technical feature of treating a subject having a pain disorder comprising administering to the subject a modulator of polypeptide activity which is not required by the other methods of Groups 129-160.

Continuation of B. FIELDS SEARCHED Item 3:
MEDLINE, CAPLUS, SCI SEARCH, BIOSIS, U.S. PATENT DATABASE, PCTFULL
search terms: dgk-e, dgk-epsilon, diacylglycerol kinase epsilon, animal model, pain, treatment