Abstract:
The invention provides genes as predictive biomarkers of statin-induced muscle toxicity. Following statin administration, three types of skeletal muscle (soleus, gastrocnemius and extensor digitorum lateralis (EDL)), including fast-twitching and slow-twitching, were profiled and analyzed. Remarkably, for samples exhibiting myopathy, the three muscle types showed highly similar gene expression profiles. Genes involved in oxidation, apoptosis, and ubiquitin-dependent protein catabolism and protein degradation were significantly changed, suggesting extensive protein degradation. In addition, significant induction of genes involved in the regulation of glycolysis and fatty acid oxidation, such as PDK4, 6-phosphofructo-2-kinase, and acetyl-Coenzyme A carboxylase beta, were also observed. PDK4 phosphatases and inactivates the pyruvate dehydrogenase complex, and is the key inducer of the metabolic switch from glycolysis to fatty acid oxidation.


Declaration under Rule 4.17:
— as to applicant’s entitlement to apply for and be granted a patent (Rule 4.17(U))

Published:
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

Date of publication of the international search report:
20 September 2007

For two-letter codes and other abbreviations, refer to the “Guidance Notes on Codes and Abbreviations” appearing at the beginning of each regular issue of the PCT Gazette.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/505 A61P/00 601N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. RELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A61K A61P GOIN

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, BIOSIS, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<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>
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</table>

X Further documents are listed in the continuation of Box C

\( ^\times \) Special categories of cited documents

\( ^\times \) later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\( ^\times \) document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\( ^\times \) document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents such combination being obvious to a person skilled in the art

\( ^\times \) document member of the same patent family

Date of the actual completion of the international search
13 April 2007

Date of mailing the international search report
30/07/2007

Name and mailing address of the ISA/Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV RUISWIJK
Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016

Jakobs, Andreas

Form PCT/ISA/210 (second sheet) (April 2005)
<table>
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<tr>
<th>Category</th>
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</table>
INTERNATIONAL SEARCH REPORT

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

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

   Although claims 9,15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition

2. Claims Nos. because they relate to parts of the International Application that do not comply with the presented requirements to such an extent that no meaningful International Search can be carried out, specifically

3. Claims Nos. because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6 4(a)

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows

   see additional 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.

   see annex

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/SA/21 0 (continuation of first sheet (2)) (January 2004)
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-9, 15

Use of statin in the manufacture of a medicament for the treatment of a cardiovascular disorder in a selected patient population, wherein the patient population is selected on the basis of the gene expression of biomarkers of statin-induced muscle toxicity by the patients following administration of statin to the patients

2. claims: 10-14

A method for diagnosing a propensity for muscle toxicity in a subject, comprising the steps of:
(a) administering a statin to the subject;
(b) determining the gene expression pattern of the subject; and
(c) determining whether the gene expression of biomarkers of statin-induced muscle toxicity by the subject indicates a propensity for muscle toxicity.