The present invention provides genetically modified host cells and use of same for producing isoprenoid compounds.
INTERNATIONAL SEARCH REPORT

A CLASSIFICATION OF SUBJECT MATTER

IPC C12N 1/00 (2006 01)

USPC 435/44.67

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

B FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

US 435/44.67

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 practicable, search terms used)

EAST, PUBMED

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>
</tr>
</thead>
</table>

D Further documents are listed in the continuation of Box C

| "" | See patent family annex |
| "" | |
| "T" | 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 |
| "X" | 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 |
| "Y" | 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 |
| "E" | |

Date of the actual completion of the international search
10 June 2008 (10 06 2008)

Name and mailing address of the ISA/US
Mail Stop PCT, Attn ISA/US
Commissioner for Patents
P O Box 1450
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Date of mailing of the international search report
14 AUG 2008

Form PCT/ISA/2 (second sheet) (April 2007)
# INTERNATIONAL SEARCH REPORT

## 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

2. **Claims 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. **Claims Nos**
   - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

## 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:

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 additional fees, this Authority did not invite payment of any additional fees**

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

### Remark on Protest

- **The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee**
- **The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation**
- **No protest accompanied the payment of additional search fees**

Form PCT/ISA/210 (continuation of first sheet(2)) (April 2007)
BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

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

Group I, claim(s) 1-10, drawn to a host cell capable of producing an isoprenoid, said host cell comprising at least two coding regions comprising nucleotide sequences encoding a mevalonate kinase, a nucleic acid comprising a nucleotide sequence encoding one or more mevalonate pathway enzymes other than mevalonate kinase, and a heterologous nucleic acid comprising a nucleotide sequence encoding a terpene synthase.

Group II, claim(s) 11-17, drawn to a host cell capable of producing an isoprenoid and comprising a coding region encoding a mevalonate kinase (MK), wherein the MK coding region is under the control of a first promoter, a nucleic acid comprising a nucleotide sequence encoding one or more mevalonate pathway enzyme other than mevalonate kinase under the control of a second promoter wherein the second promoter is weaker than the first promoter, and a heterologous nucleotide sequence encoding a terpene synthase.

Group III, claim(s) 18-20, drawn to an Escherichia coli host cell capable of producing an isoprenoid and comprising a first expression plasmid comprising a nucleotide sequence encoding a mevalonate kinase, a second expression plasmid comprising a nucleotide sequence encoding one or more MEV pathway enzymes other than mevalonate kinase wherein the copy number of the second expression plasmid is lower than that of the first expression plasmid, and a heterologous nucleotide sequence encoding a terpene synthase.

The inventions listed as Groups I-III 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. The technical feature Unking the invention first claimed is a recombinant host cell comprising various genes encoding enzymes in the mevalonate pathway in addition to a gene encoding a terpene synthase. However Martin et al teach recombinant E. coli host cells comprising heterologous set of genes encoding mevalonate pathway genes and an amorphadiene synthase gene (which is a terpene synthase gene). Therefore the technical feature taught is not a special technical feature as required by PCT RULE 13.1 as it does not contribute to the prior art.

Form PCT/ISA/210 (extra sheet) (April 2007)