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(81) Designated States (unless otherwise indicated, for every

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(54) Title: GENETICALLY ENGINEERED PLANTS FOR INCREASED PRODUCTION OF VINDOLINE

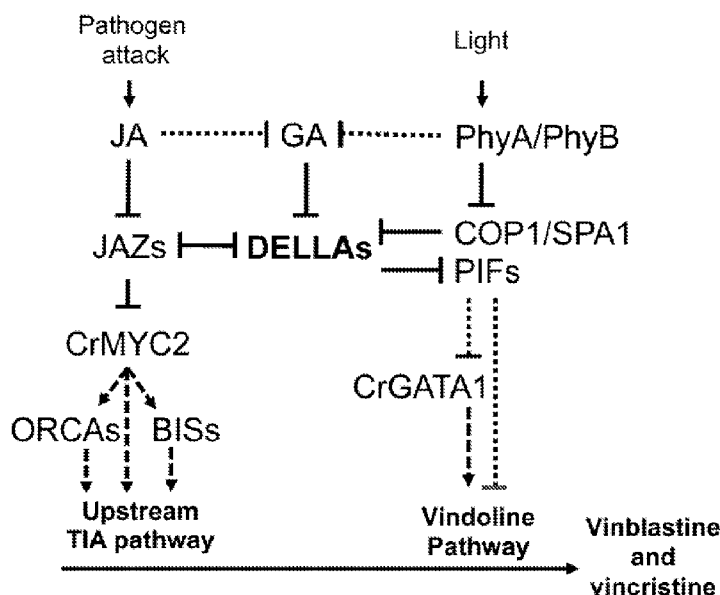


Fig. 1A

(57) **Abstract:** Two novel transcription factors, CrDELLA1 and CrDELLA2, are described in *Catharanthus roseus* plants. The DELLA transcription factors have a regulatory role in the synthesis of vinblastine and vincristine, two important anti-cancer compounds that have proved difficult to obtain in sufficient quantities. The present technology provides genetically modified *C. roseus* plants having enhanced DELLA activity, which leads to activation of multiple enzymes in the biosynthetic pathway leading to vinblastine and vincristine. The genetic modifications can be used together with activation of plant defense mechanisms and responses to light in order to boost vinblastine and vincristine synthesis.





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Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
- *of inventorship (Rule 4.17(iv))*

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) **Date of publication of the international search report:**

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/018093

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - INV. - A01H 6/08; A01H 1/02; A01H 1/06; C12N 5/04; C12P 17/10 (2023.01)

ADD.

CPC - INV. - A01H 6/084; A01H 1/02; A01H 1/06; A01H 1/12; C12P 17/10 (2023.08)

ADD. - C12N 5/04 (2023.08)

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)

See Search History document

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

See Search History document

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2019/219933 A1 (VIB VZW et al.) 21 November 2019 (21.11.2019) entire document	1-4, 17-19
Y	RIZVI, Genetic engineering of Catharanthus roseus to enhance production of anticancer pharmaceutical compounds, Northeastern University, 17 April 2015, [retrieved on 12.09.23], Retrieved from the internet: <URL:https://repository.library.northeastern.edu/files/neu:rx915f37w/fulltext.pdf>. entire document	1-4, 17-19
A	US 2009/0165167 A1 (GOOSSENS et al.) 25 June 2009 (25.06.2009) entire document	1-4, 17-19
A	LIU et al., Terpenoid indole alkaloid biosynthesis in Catharanthus roseus: effects and prospects of environmental factors in metabolic engineering, Biotechnical Letters, Vol. 43, 25 September 2021, Pgs. 2085-2103. entire document	1-4, 17-19

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"&" document member of the same patent family

Date of the actual completion of the international search

13 September 2023

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/018093

Box No. 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:
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.: 5-16, 20-31
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. 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:

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 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.