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A61K 31/4192 (2006.01) A61P 35/00 (2006.01)  
A61K 47/55 (2017.01)

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English

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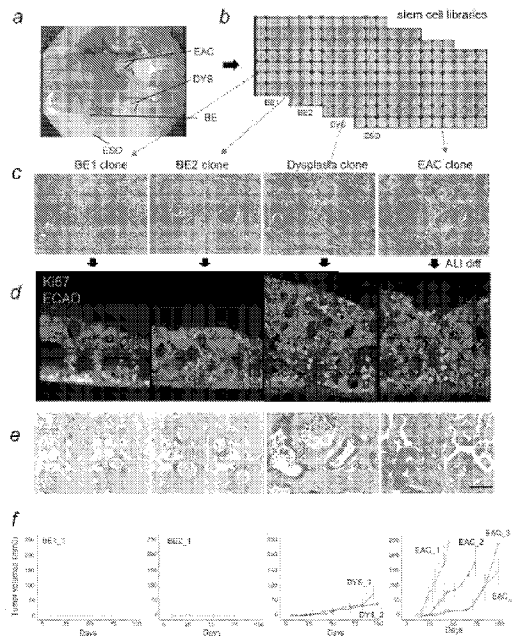
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE,

(54) Title: METHODS AND COMPOSITIONS FOR TREATING CHRONIC INFLAMMATORY INJURY, METAPLASIA, DYSPLASIA AND CANCERS OF EPITHELIAL TISSUES



FIGS. 1A-F

(57) Abstract: The present disclosure provides methods and formulations for treating a patient suffering from one or more of chronic inflammatory injury, metaplasia, dysplasia or cancer of esophageal tissue and gastric tissue, which method comprises administering to the patient an agent that selectively kills or inhibits the proliferation or differentiation of pathogenic Barrett's Esophagus stem cells (BESCs) or Gastric Intestinal Metaplasia stem cells (GIMSCs) relative to normal regenerative esophageal stem cells or gastric stem cells in the tissue in which the BESCs or GIMSCs are found.



KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

**(84) Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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- *with international search report (Art. 21(3))*
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04 April 2024 (04.04.2024)

**INTERNATIONAL SEARCH REPORT**

International application No  
**PCT/US2022/078542**

**A. CLASSIFICATION OF SUBJECT MATTER**  
**INV. A61K31/5025 A61K31/4192 A61K47/55 A61P1/00 A61P35/00**  
**ADD.**

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)  
**A61K A61P**

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)  
**EPO-Internal, CHEM ABS Data**

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
<b>Y</b>	<b>WO 2021/175326 A1 (BEIJING SINOTAU BIO PHARMACEUTICALS TECH CO LTD [CN]) 10 September 2021 (2021-09-10) the whole document</b>	<b>1-41, 45</b>
<b>Y</b>	<b>SUN HAIYING ET AL: "Design, Synthesis, and Characterization of a Potent, Nonpeptide, Cell-Permeable, Bivalent Smac Mimetic That Concurrently Targets Both the BIR2 and BIR3 Domains in XIAP", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 129, no. 49, 14 November 2007 (2007-11-14), pages 15279-15294, XP093112919, ISSN: 0002-7863, DOI: 10.1021/ja074725f the whole document</b>	<b>1-41, 45</b>

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
  - "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 <b>12 January 2024</b>	Date of mailing of the international search report <b>12/03/2024</b>
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer <b>Moutafidou, Nikoleta</b>
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2022/078542

## 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.:  
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:

**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 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.:  
**1-41, 45**

### 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.

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2022/078542

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2020/219963 A1 (UNIV HOUSTON SYSTEM [US]; UNIV TEXAS [US] ET AL.) 29 October 2020 (2020-10-29) page 119; claims; figure 1 -----	1-41, 45
X	RU 2 696 310 C1 (ASTEKS TERAPYUTIKS LTD [GB]) 1 August 2019 (2019-08-01)	1-8, 16, 17, 22, 23, 26-29, 31, 32, 45
Y	the whole document -----	1-41, 45
X	WO 2013/043591 A1 (EINSTEIN COLL MED [US]; LIBUTTI STEVEN K [US]; YUAN ZIQIANG [US]) 28 March 2013 (2013-03-28)	1-3, 5-7, 16, 17, 22, 23, 26-29, 31, 32
Y	the whole document -----	1-41, 45
X	DIZDAR LEVENT ET AL: "Clinicopathological and functional implications of the inhibitor of apoptosis proteins survivin and XIAP in esophageal cancer", ONCOLOGY LETTERS, 9 January 2018 (2018-01-09), XP093113155, GR ISSN: 1792-1074, DOI: 10.3892/ol.2018.7755	1-3, 5-7, 16, 17, 22, 23, 26-29, 31, 32
Y	the whole document -----	1-41, 45
A	DE FALCO VALENTINA ET AL: "Ponatinib (AP24534) Is a Novel Potent Inhibitor of Oncogenic RET Mutants Associated With Thyroid Cancer", JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, vol. 98, no. 5, 1 May 2013 (2013-05-01), pages E811-E819, XP093113394, US ISSN: 0021-972X, DOI: 10.1210/jc.2012-2672 the whole document -----	1-41, 45

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2022/078542

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2021175326 A1	10-09-2021	CN 115243719 A	25-10-2022
		EP 4115902 A1	11-01-2023
		JP 2023518132 A	27-04-2023
		US 2023112450 A1	13-04-2023
		WO 2021175326 A1	10-09-2021
WO 2020219963 A1	29-10-2020	AU 2020263577 A1	18-11-2021
		CA 3135020 A1	29-10-2020
		CN 114007671 A	01-02-2022
		EP 3962559 A1	09-03-2022
		IL 287573 A	01-12-2021
		JP 2022529535 A	22-06-2022
		KR 20220007867 A	19-01-2022
		US 2022202792 A1	30-06-2022
		WO 2020219963 A1	29-10-2020
		RU 2696310 C1	01-08-2019
AU 2019200840 A1	28-02-2019		
BR 112016014561 A2	08-08-2017		
BR 122022015241 B1	26-09-2023		
CA 2933939 A1	25-06-2015		
CN 105829310 A	03-08-2016		
CN 109336883 A	15-02-2019		
CN 115368356 A	22-11-2022		
CY 1124436 T1	22-07-2022		
DK 3083616 T3	30-08-2021		
EP 3083616 A1	26-10-2016		
EP 3686200 A2	29-07-2020		
ES 2883289 T3	07-12-2021		
HR P20211406 T1	10-12-2021		
HU E056297 T2	28-02-2022		
JP 6470756 B2	13-02-2019		
JP 6735369 B2	05-08-2020		
JP 7110279 B2	01-08-2022		
JP 2017500338 A	05-01-2017		
JP 2019070030 A	09-05-2019		
JP 2020183409 A	12-11-2020		
KR 20160095160 A	10-08-2016		
LT 3083616 T	10-09-2021		
MY 186311 A	08-07-2021		
MY 193649 A	21-10-2022		
NZ 719905 A	25-10-2019		
NZ 758528 A	27-05-2022		
PH 12016501139 A1	18-07-2016		
PL 3083616 T3	06-12-2021		
PT 3083616 T	12-08-2021		
RS 62301 B1	30-09-2021		
RU 2016129472 A	25-01-2018		
SG 10201808102W A	30-10-2018		
SG 11201604795R A	28-07-2016		
SI 3083616 T1	31-12-2021		
TW 201609724 A	16-03-2016		
US 2017029419 A1	02-02-2017		
US 2018065959 A1	08-03-2018		
US 2020325134 A1	15-10-2020		
US 2022204503 A1	30-06-2022		
US 2023227450 A1	20-07-2023		
WO 2015092420 A1	25-06-2015		

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

**PCT/US2022/078542**

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
<hr/> <b>WO 2013043591</b> <hr/>	<b>A1</b>	<b>28-03-2013</b>	<b>NONE</b> <hr/>

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-41, 45

Use of IAP inhibitors and devices comprising them, for treating conditions of esophageal tissue.

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2. claim: 42

A bioadhesive nanoparticle per se.

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3. claim: 43

A submucosal retentive formulation per se.

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4. claim: 44

An injectable thermogel per se.

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5. claim: 46

A formulation comprising an IAP inhibitor agent and an ESO Regenerative agent per se.

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