



(12) Translation of
European patent specification

(11) NO/EP 2892330 B1

NORWAY

(19) NO

(51) Int Cl.

A01K 67/027 (2006.01)

A01K 39/00 (2006.01)

Norwegian Industrial Property Office

(45)	Translation Published	2023.03.20
(80)	Date of The European Patent Office Publication of the Granted Patent	2022.11.23
(86)	European Application Nr.	13834735.6
(86)	European Filing Date	2013.09.06
(87)	The European Application's Publication Date	2015.07.15
(30)	Priority	2012.09.07, US, 201261698002 P 2013.03.08, US, 201361775171 P
(84)	Designated Contracting States:	AL; AT; BE; BG; CH; CY; CZ; DE; DK; EE; ES; FI; FR; GB; GR; HR; HU; IE; IS; IT; LI; LT; LU; LV; MC; MK; MT; NL; NO; PL; PT; RO; RS; SE; SI; SK; SM; TR
(73)	Proprietor	Yale University, Two Whitney Avenue, New Haven, CT 06510, USA Institute for Research in Biomedicine (IRB), Via Vincenzo Vela 6, 6501 Bellinzona, Sveits Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591-6707, USA
(72)	Inventor	FLAVELL, Richard, A., 283 Moose Hill Road, Guilford, CT 06437, USA MANZ, Markus, Stettbachstrasse 9, CH-8702 Zollikon, Sveits RONGVAUX, Anthony, 153 Cold Spring Street, New Haven, CT 06511, USA STROWIG, Till, 20 Tilton Street, New Haven, CT 06511, USA WILLINGER, Tim, Mosstenabacken 13, lgh 1104, 124 32 Bandhagen, Sverige YANCOPOULOS, George, 1519 Baptist Church Road, Yorktown Heights, NY 10598, USA STEVENS, Sean, 3954 Camino Calma, San Diego, CA 92122, USA MURPHY, Andrew, J., 10 Newton Court, Croton-on-Hudson, NY 10520, USA
(74)	Agent or Attorney	ZACCO NORWAY AS, Postboks 488, 0213 OSLO, Norge

(54)	Title	GENETICALLY MODIFIED MICE AND METHODS OF USE THEREOF
------	-------	---

(56) References

Cited:

WO-A2-2014/071397, US-A1- 2012 157 667, WO-A2-2012/040207, US-A1- 2011 200 982,
GARCIA SYLVIE ET AL: "Humanized mice: Current states and perspectives", IMMUNOLOGY
LETTERS, ELSEVIER BV, NL, vol. 146, no. 1-2, 30 August 2012 (2012-08-30), pages 1-7,
XP002681730, ISSN: 0165-2478, DOI: 10.1016/J.IMLET.2012.03.009
ANTHONY RONGVAUX ET AL: "Development and function of human innate immune cells in a
humanized mouse model", NATURE BIOTECHNOLOGY, 2014 APRIL, vol. 32, no. 4, April 2014
(2014-04), pages 364-372, XP055112690, ISSN: 1087-0156, DOI: 10.1038/nbt.2858
A. P. A. THEOCHARIDES ET AL: "Disruption of SIRP signaling in macrophages eliminates
human acute myeloid leukemia stem cells in xenografts", BLOOD, vol. 119, no. 18, 3 September
2012 (2012-09-03), pages 4333-1899, XP055126663, ISSN: 0006-4971, DOI: 10.1182/blood-
2011-11-391367

RONGVAUX, A. ET AL: "W72.004. MISTRG: a novel humanised mouse model to study human hematopoiesis and myeloid development and function in vivo", IMMUNOLOGY. ABSTRACTS FROM THE ANNUAL CONGRESS OF THE BRITISH SOCIETY FOR IMMUNOLOGY. NOVEMBER 17-21, 2008. GLASGOW, UNITED KINGDOM., vol. 137, no. suppl.1, 5 September 2012 (2012-09-05), page 184, XP002758760, DOI: 10.1111/imm.12001 & European Congress of Immunology 5-8 September 2012 Glasgow. Workshop: Humanised Mice

TILL STROWIG ET AL: "Transgenic expression of human signal regulatory protein alpha in Rag2(-/-)gamma(-/-)(c) mice improves engraftment of human hematopoietic cells in humanized mice + Supplementary Online Data", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, NATIONAL ACADEMY OF SCIENCES, US, vol. 108, no. 32, 9 August 2011 (2011-08-09), pages 13218-13223, XP002681726, ISSN: 0027-8424, DOI: 10.1073/PNAS.1109769108

R. W. J. GROEN ET AL: "Reconstructing the human hematopoietic niche in immunodeficient mice: opportunities for studying primary multiple myeloma", BLOOD, vol. 120, no. 3, 31 May 2012 (2012-05-31), pages e9-e16, XP055113167, ISSN: 0006-4971, DOI: 10.1182/blood-2012-03-414920

TIM WILLINGER ET AL: "Improving human hemato-lymphoid-system mice by cytokine knock-in gene replacement", TRENDS IN IMMUNOLOGY, 2011 JULY, vol. 32, no. 7, 21 June 2011 (2011-06-21), pages 321-327, XP028238170, ISSN: 1471-4906, DOI: 10.1016/J.IT.2011.04.005 [retrieved on 2011-04-21]

Enclosed is a translation of the patent claims in Norwegian. Please note that as per the Norwegian Patents Acts, section 66i the patent will receive protection in Norway only as far as there is agreement between the translation and the language of the application/patent granted at the EPO. In matters concerning the validity of the patent, language of the application/patent granted at the EPO will be used as the basis for the decision. The patent documents published by the EPO are available through Espacenet (<http://worldwide.espacenet.com>) or via the search engine on our website here: <https://search.patentstyret.no/>

EP2892330

1

Patentkrav**1.** Genmodifisert mus omfattende i dens genom:

5 en nukleinsyre som koder for humant M-CSF som erstatter nukleinsyren som koder for muse-M-CSF og operativt koplet til muse-M-CSF-promotoren og regulatoriske elementer, en nukleinsyre som koder for humant IL-3 som erstatter nukleinsyren som koder for muse-IL-3 og operativt koplet til muse-IL-3-promotoren og regulatoriske elementer, en nukleinsyre som koder for humant GM-CSF som erstatter nukleinsyren som koder for muse-GM-CSF og operativt koplet til muse-GM-CSF-promotoren og regulatoriske elementer, en nukleinsyre som koder for humant SIRPA operativt koplet til en human SIRPA-promotor og human SIRPA-regulatorisk sekvens, og en nukleinsyre som koder for human TPO som erstatter nukleinsyren som koder for muse-TPO og operativt koplet til muse-TPO-promotoren og regulatoriske elementer, hvori musen uttrykker
10 humant M-CSF-polypeptid, humant IL-3-polypeptid, humant GM-CSF-polypeptid, humant SIRPA-polypeptid og humant TPO-polypeptid, og hvori musen omfatter en rekombinasjonsaktiverende gen 2 (Rag2) genknock-out og en IL2-reseptorgammakjede (IL2rg) gen knock-out.

20 **2.** Den genmodifiserte musen ifølge krav 1, også omfattende humane hematopoietiske celler.

3. Den genmodifiserte musen ifølge krav 1 eller 2, også omfattende en human kreftcelle.

25 **4.** Den genmodifiserte musen ifølge krav 3, hvori den humane kreftcellen er en leukemicelle eller en melanomcelle.

5. Fremgangsmåte for innpodning av hematopoietisk stam- og progenitorcelle (HSPC) i en genmodifisert mus, hvori musen uttrykker humant M-CSF, humant IL-3, humant GM-CSF, humant SIRPA og humant TPO, fremgangsmåten omfattende trinnet: administrering av minst én HSPC til den genmodifiserte
30

EP2892330

2

musen ifølge krav 1.

6. Fremgangsmåten ifølge krav 5, hvori den genmodifiserte musen omfatter en human kreftcelle.

5

7. Fremgangsmåten ifølge krav 6, hvori den humane kreftcellen er en leukemicelle eller en melanomcelle.