Trial decision

Invalidation No. 2014-800093

USA Appellant	AKEBIA THERAPEUTICS INC
Tokyo, Japan Attorney	MIMURA, Ryoichi
Tokyo, Japan Attorney	TOSAKI, Kenji
Tokyo, Japan Patent Attorney	NANJO, Masahiro
Tokyo, Japan Patent Attorney	HARA, Hokuto
Tokyo, Japan Patent Attorney	SETA, Ayako
USA Demandee	FIBROGEN, INC
Tokyo, Japan Patent Attorney	HIRAKI, Yusuke
Tokyo, Japan Patent Attorney	FUJITA, Takashi
Tokyo, Japan Patent Attorney	TANAKA, Natsuo
Tokyo, Japan Patent Attorney	KIKUTA, Naoko
Tokyo, Japan Patent Attorney	NOMURA, Wakako
Tokyo, Japan Patent Attorney	EJIMA, Koki
Tokyo, Japan Patent Attorney	OBARA, Atsushi

The case of trial for invalidation of Japanese Patent No. 4804131, entitled "Method of increasing endogenous erythropoietin (EPO)" between the parties above has resulted in the following trial decision:

[Conclusion]

The correction shall be approved as requested.

The demand for trial of the case was groundless.

The costs in connection with the trial shall be borne by the demandant.

Reason

No. 1 History of the procedures

The present application according to Japanese Patent No. 4804131 (the number of claims is 10. Hereinafter referred to as the "Patent") is a divisional application (foreign language application) filed on December 5, 2005 from Japanese Patent Application No. 2003-554713 filed on December 6, 2002 as an international filing date (priority claim under the Paris Convention: December 6, 2001, January 16, 2002, February 25, 2002 and June 5, 2002 (US)), and the establishment of the patent right was registered on August 19, 2011.

The demandant demanded trial for patent invalidation, regarding the inventions according to claims 1, and 5 to 10 of the Patent, on June 3, 2014 (accepted by Japan Patent Office).

The history of the procedures of trial for invalidation of the case is as follows:

June 3, 2014 written demand for trial, and Evidence A No. 1 to A No. 23 and the translations of Evidence A No. 1 to A No. 4, A No. 6, A No. 7, A No. 9 to A No. 12, A No. 17, A No. 18, A No. 20 to A No. 22

September 22, 2014 written reply, and Evidence B No. 1 to B No. 15 and the translations of Evidence B No. 1, B No. 2, B No. 4 to B No. 15, A No. 1 to A No. 4, A No. 7, A No. 10 to A No. 12

December 11, 2014 notification of trial examination (drafting date)

January 26, 2015 oral proceedings statement brief (demandant), and Evidence A No. 24 to A No. 33 and the translations of Evidence A No. 25 to A No. 33

January 26, 2015 oral proceedings statement brief (demandee) and Evidence B No. 16 to B No. 19

February 6, 2015 written statement (demandant) and Evidence A No. 34

February 9, 2015 oral proceeding

February 13, 2015 written statement (demandant) and Evidence A No. 35 to A No. 38

February 24, 2015 written statement (demandee) and the translations of Evidence A No. 9, A No. 10, A No. 26 to A No. 29, A No. 31, A No. 33

May 11, 2015 advance notice of a trial decision (drafting date)

August 11, 2015 written correction request and written statement (demandee)

October 9, 2015 written refutation (demandant)

No. 2 Suitability of correction

1 Matters of correction

Correction requested by the demandee (hereinafter referred to as "Correction of the case") is to correct the description, the scope of claims, and drawings of Japanese Patent No. 4804131 to the description, the scope of claims, and drawings attached to the written correction request submitted on August 11, 2015 for each group of claims.

Matters of correction are to delete, in claim 1 according to the scope of claims, "R^1, R^2 and R^3 are each independently selected from the group consisting of hydrogen, halogen, cyano, (C_1-C_{20})-alkyl, (C_1-C_{20})-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy, carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N-((C_1-C_{18})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, or -O-$[CH_2]_xC_fH_{(2f+1-g)}F_g$ (where f is 1, g is 3, and x is 0); where an aryl radial may be substituted by 1 to 5 substituents selected from halogen, cyano, (C_2-C_{16})-alkyl, (C_1-C_{16})-alkoxy and carbamoyl; or wherein,".

2 Suitability of purpose of correction, existence or absence of addition of new matter, existence or absence of substantial expansion or change of the scope of claims, and independent requirements for patentability

(1) Purpose of Correction

The Correction of the case is, in claim 1, to delete "R^1, R^2 and R^3 are each

independently selected from the group consisting of hydrogen, halogen, cyano, (C_1-C_{20})-alkyl, (C_1-C_{20})-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy, carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N-((C_1-C_{18})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, or -O-$[CH_2]_xC_fH_{(2f+1-g)}F_g$ (where f is 1, g is 3, and x is 0); where an aryl radial may be substituted by 1 to 5 substituents selected from halogen, cyano, (C_2-C_{16})-alkyl, (C_1-C_{16})-alkoxy and carbamoyl; or wherein," from the definition of substituents R^1 to R^3 in formula (I) representing a heterocyclic carboxamide compound, so as to limit substituents R^1 to R^3 in the compound represented by formula (I) to heterocycle systems represented by formula (Ia) or (Ib), together with pyridine carrying the substituents. Therefore, the Correction of the case is for the purpose of restriction of the scope of claims in accordance with item (i) of the proviso to Article 134-2(1) of the Patent Act.

(2) Existence or absence of addition of new matter

As it is clear from the reason described in (1) above, the Correction of the case is to delete a part of choices of substituents in the compound represented by formula (I), not to add a new matter.

Therefore, the Correction of the case is within the scope of the matters described in the description, the scope of claims, or drawings, and falls under the provision of Article 126(5) of the Patent Act which is applied mutatis mutandis pursuant to the provisions of Article 134-2(9).

(3) Existence or absence of substantial expansion or change of the scope of claims

As is clear from the reason described in (1) above, the Correction of the case is to delete a part of choices of substituents in the compound represented by formula (I), not to change category, target, and purpose of the invention. Therefore, the Correction of the case does not substantially enlarge or change the scope of claims, and falls under the provision of Article 126(6) of the Patent Act which is applied mutatis mutandis pursuant to the provisions of Article 134-2(9).

(4) Independent requirements for patentability

As the Correction of the case is to correct claim 1 according to the scope of claims, and claims 2 to 8, and 10 are dependent on claim 1 to be corrected, claims 1 to 8, and 10 are a group of claims. Further, as claim 9 is dependent on claim 8 which is dependent on claim 1 to be corrected, claims 1, 8, and 9 are a group of claims.

Therefore, claims 1 to 10 are a group of claims. On the other hand, as described in 1 above, the Correction of the case is to request to correct the scope of claims to each group of claims. As described in No. 1 above, as claims in which the demandant demands for invalidation are claims 1, and 5 to 10, claims 2 to 4 according to the scope of claims fall under "claims in which trial for invalidation is not demanded" provided in Article 126(7) of the Patent Act which is applied mutatis mutandis pursuant to the provisions of Article 134-2(9).

Claims 2 to 4 before Correction of the case are as follows:

"[Claim 2] The use of claim 1, wherein the heterocyclic carboxamide compound is represented by formula Ia, wherein R^{13} is hydrogen, (C_1-C_{20})-alkyl, (C_1-C_{20})-alkoxy, (C_6-C_{12})-aryloxy, or -O-$[CH_2]_xC_fH_{(2f+1-g)}F_g$ (where f is 1, g is 3, and x is 0); R^{14} is hydrogen or halogen.

[Claim 3] The use of claim 1, wherein the heterocyclic carboxamide compound is represented by formula Ib, wherein R^3 is hydrogen or halogen; R^{17} is hydrogen; and R^{18} is hydrogen, (C_1-C_{20})-alkyl, (C_1-C_{20})-alkoxy, (C_6-C_{12})-aryloxy, or -O-$[CH_2]_xC_fH_{(2f+1-g)}F_g$ (where f is 1, g is 3, and x is 0).

[Claim 4] The use of claim 1, wherein the heterocyclic carboxamide compound is selected from the group consisting of [(3-benzyloxy-7-chloro-quinoline-2-carbonyl)-amino]-acetic acid, [(3-hydroxy-6-isopropoxy-quinoline-2-carbonyl)-amino]-acetic acid, [(3-hydroxy-6-phenoxy-quinoline-2-carbonyl)-amino]-acetic acid, [(3-hydroxy-6-trifluoromethoxy-quinoline-2-carbonyl)-amino]-acetic acid, [(1-chloro-4-hydroxyisoquinoline-3-carbonyl)-amino]-acetic acid, [(4-Hydroxy-7-isopropoxy-isoquinoline-3-carbonyl)-amino]-acetic acid, [(7-butoxy-4-hydroxy-isoquinoline-3-carbonyl)-amino]-acetic acid, N-((1-chloro-4-hydroxy-7-methoxyisoquinolin-3-yl)-carbonyl)-glycine, and [(1-Chloro-4-hydroxy-7-isopropoxy-isoquinoline-3-carbonyl)-amino]-acetic acid."

These claims limit the substituents R^1 to R^3 in the heterocyclic carboxamide compound represented by formula (I) in claim 1, to a case where the compound is represented by formula Ia or Ib, together with pyridine carrying the substituents; however, the Correction of the case does not change the range with respect to the substituents in formulas Ia and Ib before and after the Correction, so that the ranges of claims 2 to 4 before and after the Correction of the case do not change.

That is to say, even though it is formally treated that claims 2 to 4 are requested for correction, as the matters specifying the invention do not change before and after the Correction of the case, the correction of claims 2 to 4 is not for the purpose of restriction of the scope of claims, or correction of errors or incorrect translations.

Therefore, claims 2 to 4 according to the scope of claims are not applied to the provisions of Article 126(7) of the Patent Act which is applied mutatis mutandis pursuant to the provisions of Article 134-2(9).

(5) Summary

The Correction of the case is for the purpose of restriction of the scope of claims, not to add a new matter and substantially enlarge or change the scope of claims.

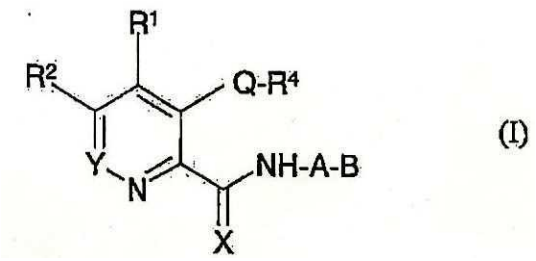
Therefore, the Correction of the case shall be approved.

No. 3 Corrected invention of the case

As described above, the inventions according to claims 1, and 5 to 10 of the Patent are specified as follows, as viewed from the description attached to the written correction request (hereinafter referred to as the "corrected description"), and the corrected scope of claims and drawings, in accordance with the matter described in claims 1, and 5 to 10 according to the scope of claims.

[Claim 1] Use of a heterocyclic carboxamide compound for manufacturing an agent for treating anemia in a subject, wherein the heterocyclic carboxamide compound inhibits HIF prolyl hydroxylase, and is represented by formula (I) or a physiologically active salt derived therefrom

[Chemical 1]



(I)

[where,

A is $-CH_2-$;

B is -CO_2H or CO_2-G carboxyl radical (where G is a radical of alcohol G-OH in which G is (C_1-C_{20})-alkyl radical or (C_7-C_{16})-carbocyclic aralkyl radical);

X is O;

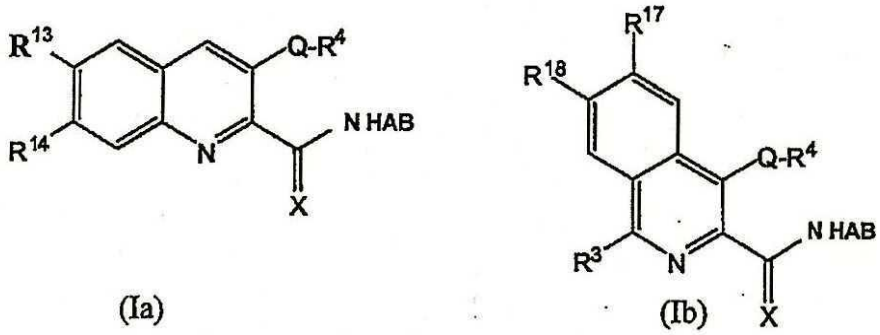
Q is O;

R^4 is hydrogen or benzyl;

Y is CR^3;

R^1 and R^2, or R^2 and R^3, together with the pyridine carrying them, form an optionally substituted heterocycle system selected from formulas Ia and Ib,

[Chemical 2]



substituents R^3, R^{13}, R^{14}, R^{17} and R^{18} are each independently selected from the group consisting of hydrogen, halogen, cyano, (C_1-C_{20})-alkyl, (C_1-C_{20})-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy, carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N-((C_1-C_{18})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, or -O-$[CH_2]_xC_fH_{(2f+1-g)}F_g$ (where f is 1, g is 3, and x is 0); where an aryl radial may be substituted by 1 to 5 substituents selected from halogen, cyano, (C_2-C_{16})-alkyl, (C_1-C_{16})-alkoxy and carbamoyl].

[Claim 5] The use of claim 1, wherein the anemia is associated with abnormal hemoglobin or erythrocyte.

[Claim 6] The use of claim 1, wherein the anemia is associated with a condition selected from the group consisting of diabetes, cancer, ulcers, kidney disease, immunosuppressive disease, infection, and inflammation.

[Claim 7] The use of claim 1, wherein the anemia is associated with a procedure or treatment selected from the group consisting of radiation therapy, chemotherapy, dialysis, and surgery.

[Claim 8] The use of claim 1, wherein the anemia is associated with blood loss.
[Claim 9] The use of claim 8, wherein the blood loss is associated with bleeding disorder, trauma, injury, or surgery.
[Claim 10] The use of claim 1, wherein the anemia is associated with defect in iron transport, processing, or utilization.

(hereinafter referred to as "Corrected invention 1," "Corrected invention 5" to "Corrected invention 10," respectively)

No. 4 Overview of the party's allegation

1 Overview of the demandant's allegation

According to written demand for trial, oral proceedings statement brief, and oral proceeding record, the brief reasons for invalidation alleged by the demandant are as follows:

(1) Reason 1 for invalidation

As the Corrected inventions 1, and 5 to 10 could be easily made by a person skilled in the art on the basis of the invention described in Evidence A No. 6 and the well-known arts, the demandant should not be granted a patent for the invention in accordance with the provisions of Article 29(2) of the Patent Act (Article 123(1)(i) of the Patent Act).

(2) Reason 2 for invalidation

As the Corrected inventions 1, and 5 to 10 could be easily made by a person skilled in the art on the basis of any of the inventions described in Evidence A No. 14 to A No. 16 and the well-known arts, the demandant should not be granted a patent for the invention in accordance with the provisions of Article 29(2) of the Patent Act (Article 123(1)(i) of the Patent Act).

(3) Reason 3 for invalidation

As only examples regarding compounds whose chemical structures are extremely similar with each other are described in the detailed description of the invention, a person skilled in the art must do a lot of experiments to confirm which compounds can be used for treating anemia, and the description of the detailed description of the invention does not meet the requirement stipulated in Article 36(4)(i) of the Patent Act. Further, as there is no description, in the detailed description of the

invention, to support that billions of kinds of heterocyclic carboxamide compounds described in the scope of claims can be used for treating anemia, the description of the scope of claims does not meet the requirement stipulated in Article 36(6)(i) of the Patent Act (Article 123(1)(iv) of the Patent Act).

(4) Reason 4 for invalidation

As there is no description, in the detailed description of the invention, about examination results whether the heterocyclic carboxamide compound described in the scope of claims of the case inhibits HIF prolyl hydroxylase, the description of the detailed description of the invention does not meet the requirement stipulated in Article 36(4)(i) of the Patent Act (Article 123(1)(iv) of the Patent Act).

(5) Reason 5 for invalidation

With the amendment dated April 11, 2011, the matters described in the scope of claims of the case are not within the matters described in the document in foreign language (Article 123(1)(v) of the Patent Act).

<Evidence>

Evidence A No. 1: priority certificate regarding U.S. Patent Application No. 60/337,082 filed on December 6, 2001

Evidence A No. 2: priority certificate regarding U.S. Patent Application No. 60/349,659 filed on January 16, 2002

Evidence A No. 3: priority certificate regarding U.S. Patent Application No. 60/359,683 filed on February 25, 2002

Evidence A No. 4: priority certificate regarding U.S. Patent Application No. 60/386,488 filed on June 5, 2002

Evidence A No. 5: Examination Guidelines for Patent and Utility Model, Part IV Priority Chapter 1 Priority under the Paris Convention, July, 2004, Japan Patent Office

Evidence A No. 6: Proc. Natl. Acad. Sci. USA, 2002.10.15, Vol. 99, No. 21, pp.13459-13464.

Evidence A No. 7: Cell, 1999, Vol. 98, pp.281-284.

Evidence A No. 8: Molecular Cell Treatment, 2000, Vol. 1, No. 6, pp.539-545.

Evidence A No. 9: Blood, 2000, Vol. 96, No. 4, pp.1558-1565.

Evidence A No. 10: Annu. Rev. Cell Dev. Biol, 1999, Vol. 15, pp.551-578.

Evidence A No. 11: Cell, 2001. 10. 05, Vol. 107, pp.1-3.
Evidence A No. 12: High Alt. Med. Biol, 2001. 10. 30 (accepted by library of congress in U.S.), Vol. 2, No. 2, pp.155-163.
Evidence A No. 13: Reference Material 2 attached to the written amendment (form) dated on November 11, 2010 submitted by the demandee in procedures for appeal regarding patent application of the case
Evidence A No. 14: Japanese Unexamined Patent Application Publication No. H7-242635
Evidence A No. 15: Japanese Unexamined Patent Application Publication No. H9-124606
Evidence A No. 16: Japanese Unexamined Patent Application Publication No. H11-302257
Evidence A No. 17: Science, 2001. 04. 20, Vol. 292, pp.464-468.
Evidence A No. 18: Science, 2001. 04. 20, Vol. 292, pp.468-472.
Evidence A No. 19: response record, dated January 7, 2011, written by the examiner in procedures for appeal (examination under the provisions of Article 162 of the Patent Act) regarding patent application of the case
Evidence A No. 20: printed website of Marketwired L. P., distributed on October 5, 2010, regarding press release of Akebia Therapeutics
Evidence A No. 21: U.S. Unexamined Patent Application Publication No. 2010/0331303
Evidence A No. 22: U.S. Unexamined Patent Application Publication No. 2010/0331374
Evidence A No. 23: Examination Guidelines for Patent and Utility Model, Part III Amendments of Description, the scope of claims or drawings Section 1 New matter, June, 2010, Japan Patent Office
Evidence A No. 24: Intellectual Property High Court Decision, March 22, 2006 (2005 (Gyo KE) No. 10296)
Evidence A No. 25: declaration by Professor Gregg L. Semenza, dated January 20, 2015
Evidence A No. 26: Semenza, G. L, 'Oxygen-regulated erythropoietin gene expression'. In: Hematopoiesis, A Developmental Approach, Edited by Zon, L. I, Oxford University Press, 2001, pp.288-298.

Evidence A No. 27: Int. J. Mol. Med, 2000, Vol. 5, pp.253-259.
Evidence A No. 28: International Publication No. WO 00/74725
Evidence A No. 29: International Publication No. WO 02/089809 (issued on November 14, 2002)
Evidence A No. 30: Blood, 1972, Vol. 40, No. 5, pp.671-677.
Evidence A No. 31: Ann. N. Y. Acad. Sci, 1994, Vol. 718, pp.50-63.
Evidence A No. 32: Blood, 1995, Vol. 85, No. 10, pp.2735-2741.
Evidence A No. 33: International Publication No. WO 02/088363 (issued on November 7, 2002)
Evidence A No. 34: Tokyo High Court Decision, November 27, 1986 (1983 (Gyo KE) No. 54)
Evidence A No. 35: printed website of amazon.com Inc. regarding document information on Evidence A No. 26
Evidence A No. 36: printed website of biblio.com Inc. regarding document information on Evidence A No. 26
Evidence A No. 37: printed website of U.S. Copyright office regarding document information on Evidence A No. 26
Evidence A No. 38: printed website of PubMed regarding document information on Evidence A No. 31

2 The demandee's allegation

The demandee alleges that none of the Reasons 1 to 5 for invalidation alleged by the demandant has reasons, and submitted Evidence B No. 1 to B No. 19 as Evidence. Further, the demandee submitted the written correction request, "To request to correct the description, the scope of claims, and drawings of Japanese Patent No. 4804131 to the corrected description, the scope of claims, and drawings attached to the written request of the case each group of claims" on August 11, 2015, and alleges that the Correction of the case shall be approved and the reasons for invalidation, and on the ground of the means of proof alleged by the demandant, the Corrected inventions 1, and 5 to 10, cannot be invalidated.

< Evidence>

Evidence B No. 1: Nephrol. Dial. Transplant, 2001, Vol. 16, Suppl.5, pp.50-55.

Evidence B No. 2: Nat. Rev. Drug Discov, 2006, Vol. 5, pp.267-268.

Evidence B No. 3: news release by Astellas Pharma Inc. and FibroGen, Inc., dated July 31, 2013

Evidence B No. 4: Webster's New World Medical Dictionary, 3rd Edition, p.19 and p.226.

Evidence B No. 5: printed website of PDR. NET in which FDA drug safety communication, dated June 24, 2011, regarding agent for stimulating ertyropoiesis is described

Evidence B No. 6: J. Am. Med. Assoc, 2011, Vol. 305, No. 18, pp.1908-1909.

Evidence B No. 7: Trends Mol. Med, 2001.08, Vol. 7, No. 8, pp.345-350.

Evidence B No. 8: Pfluegers Arch.- Eur. J. Physiol, 2002, Vol. 443, pp.503-507.

Evidence B No. 9: Nat. Rev. Drug Discov, 2003, Vol. 2, pp.1-9.

Evidence B No. 10: Macdougall, I. C, Novel strategies for stimulating erythropoiesis and potential new treatments for anaemia, Lancet, Published Online 2006, DOI:10.1016/S0140-6736(06)69120-4.

Evidence B No. 11: Nephrol. Dial. Transplant, 2001, Vol. 16, pp.1745-1749.

Evidence B No. 12: printed website of Fibrogen, Inc. regarding clinical test for anemia

Evidence B No. 13: J. Am. Soc. Nephrol, 2010, Vol. 21, pp.2151-2156.

Evidence B No. 14: Guenzier, V, 'Prolyl 4-Hydroxylase inhibitor'. In: Prolyl Hydroxylase, Protein Disulfide Isomerase, and Other Structurally Related Proteins, Edited by Guzman, N. A, Marcel Dekker Inc, 1997, pp.66-77.

Evidence B No. 15: Biochem. J, 1986, Vol. 239, pp.311-315.

Evidence B No. 16: printed website of PubMed regarding document information on Evidence B No. 1

Evidence B No. 17: printed website of PubMed regarding document information on Evidence B No. 7

Evidence B No. 18: printed website of PubMed regarding document information on Evidence B No. 8

Evidence B No. 19: printed website of PubMed regarding document information on Evidence B No. 11

No. 5 Described matters in Evidence

In the evidences which had been distributed before December 6, 2002, the filing date of original patent application of the Patent (hereinafter referred to as "original filing date"), the following matters are described.

1 Evidence A No. 6

(1) Title

"Biochemical purification and pharmacological inhibition of a mammalian prolyl hydroxylase acting on hypoxia-inducible factor"

(2) Abstract

A "The product of the von Hippel-Lindau gene, pVHL, targets the α subunits of the heterodimeric transcription factor hypoxia-inducible factor (HIF) for polyubiquitination in the presence of oxygen. The binding of pVHL to HIF is governed by the enzymatic hydroxylation of conserved proline residues within peptidic motifs present in the HIFα family members." (p. 13459, lines 1 to 6 of left column,)

B "we studied the activity of a structurally diverse collection of low molecular weight inhibitors of procollagen prolyl 4-hydroxylase as potential inhibitors of HIF hydroxylase. A model compound of this series stabilized HIF in a variety of cells, leading to the increased production of its downstream target, vascular endothelial growth factor." (p. 13459, lines 9 to 14 of left column)

(3) Introduction

"Several lines of evidence suggest that the HIF prolyl hydroxylase (HIF PH) is not identical to the well-studied type I and type II mammalian prolyl hydroxylases, which modify collagen. First, the region of HIF that is hydroxylated does not resemble the $(Pro\text{-}Pro\text{-}Gly)_n$ motif that is recognized by the type I and type II prolyl hydroxylases (10-13). Second, type I and type II prolyl hydroxylases reside in the endoplasmic reticulum (ER), whereas HIF is an intracellular protein. Third, collagen prolyl hydroxylase activity is preserved under hypoxic conditions that are sufficient to inhibit HIF PH activity (16)." (p. 13459, lines 37 to 46 of left column)

(4) Materials and Methods

A "HIF Peptide Hydroxylation Assay."

"One microgram of a synthetic, N-terminally biotinylated, peptide

corresponding to HIF1α residues 556-575 (DLDLEMLAPYIPMDDDFQLR) was immobilized on 30 μl of streptavidin-agarose (Pierce) and incubated with 50 μl of RRL, various amounts of RRL-derived column fractions, or recombinant EGLN1 for 2 hr, with tumbling, at room temperature. The total reaction volume was adjusted to 200 μl with PHA buffer and, where indicated, the following cofactors were added: $FeCl_2$ (100 μM), ascorbate (2 mM), and 2-oxoglutarate (5 mM). The agarose was then washed four times with NETN [20 mM Tris-HCl (pH 8.0)/100 mM NaCl/1 mM EDTA/0.5% Nonidet P-40], and peptide hydroxylation was determined by pVHL-binding or by MS. For the former, 10 μl of ^{35}S-labeled pVHL was added in a total volume of 500 μl of EBC [50 mM Tris-HCl (pH 8.0)/120 mM NaCl/0.5% Nonidet P-40] supplemented with complete protease inhibitor mixture (Roche Molecular Biochemicals, Indianapolis) and incubated for 1 hr at 4 degrees. After four washes with NETN, bound pVHL was eluted by boiling in SDS-containing sample buffer, resolved by PAGE, and detected by autoradiography." (p. 13459, lines 17 to 36 of right column)

B "Propyl Hydroxylase Inhibitors."

"Prolyl hydroxylase inhibitors (FibroGen) were dissolved in DMSO at a stock concentration of 10 mM. For RRL activity inhibition, the RRL was preincubated with the indicated inhibitor for 15 min before use in the peptide hydroxylation assay. GST-EGLN1 was preincubated with the indicated inhibitor in 200 μl of PHA buffer for 15 min before addition of the biotinylated HIF peptide and cofactors." (p. 13461, lines 13 to 7 from the bottom of left column)

(5) Results

A Table 1 (p. 13462)

表１．プロリルヒドロキシラーゼ阻害剤

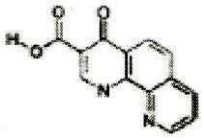
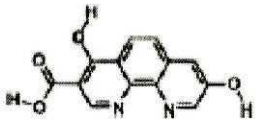
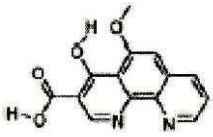
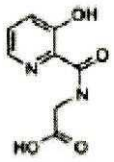
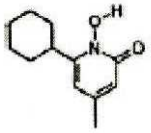
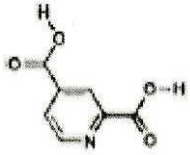
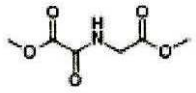
化合物番号	構造	M_r	コラーゲン　PH IC_{50}, μM
FG-0041		240.22	2
FG-1577		256.22	2
FG-1649		270.25	1
FG-2179		196.16	0.4
FG-2229		268.35	1
FG-2909		156.19	鉄濃度に依存
FG-2910		185.14	2 (K_i)
FG-2933		175.14	>30 μM
FG-2934		147.09	1–2 (K_i)

表１．プロリルヒドロキシラーゼ阻害剤 Table 1. Prolyl hydroxylase inhibitors

化合物番号 Compound no.

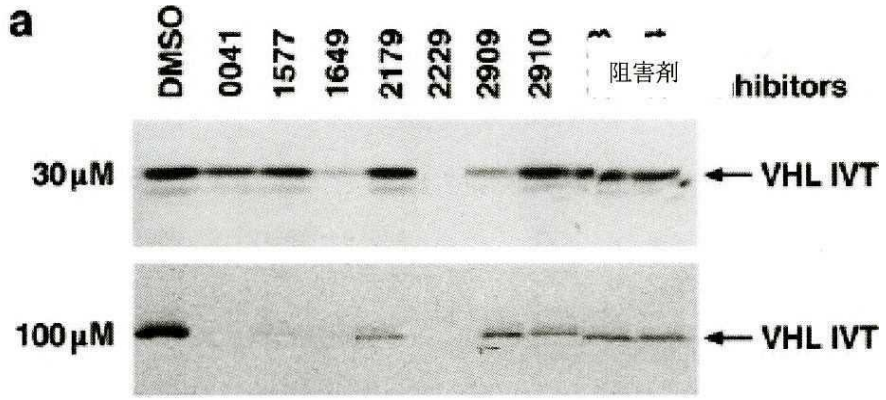
構造 Structure

コラーゲン Collagen

鉄濃度に依存 Dependent on the iron concentration

(Note by the body: It is obvious that the chemical formula of FG-2179 in Table 1 has an error about bond number of nitrogen atom in a substituent binding to 2-position of a pyridine ring, and other atoms. In a case where the description of hydrogen atom, as an atom binding to nitrogen atom in the chemical formula, is missing, molecular formula of the chemical formula is $C_8H_8N_2O_4$ and the molecular weight is 196.16. This molecular weight corresponds to the molecular weight (Mr) in Table 1. Therefore, it is recognized that the nitrogen atom in a substituent binding to 2-position of a pyridine ring in the chemical formula of FG-2179 above also binds to the hydrogen.)

B Figure 4a (p. 13462)



阻害剤 inhibitors

" Figure 4 Inhibition of EGLN1 activity by small molecules. (a) Binding of ^{35}S-labeled pVHL to biotinylated HIF (556-575) peptide, which was preincubated with RRL in the presence of the indicated compounds (see Table 1)" (p. 13462, right column, lines

1 to 3 of legend of FIG. 4)

C "A number of structurally diverse small molecule inhibitors of the collagen prolyl hydroxylases have been developed (23-27) (Table 1). Several of these compounds inhibited the HIF PH present in RRL (FIG. 4a), as well as recombinant EGLN1 (FIG. 4b and data not shown) in low micromolar concentrations." (p. 13462, lines 10 to 6 from the bottom of right column)

(6) Discussion

A "It has been suggested that stabilization of HIF through the inhibition of the HIF PH might be therapeutically beneficial in diseases characterized by acute or chronic ischemia (10, 36). Among these diseases are major causes of morbidity and mortality in the developed world, including myocardial infarction, stroke, peripheral vascular disease, and diabetes." (p. 13464, lines 1 to 6 of left column)

B "Of note, FG-0041 was shown earlier to preserve left ventricular function in a rodent model of myocardial infarction (39). This effect was initially attributed to the inhibition of collagen prolyl hydroxylase (39). However, our finding that FG-0041 inhibits HIF PH activity, coupled with the fact that the beneficial effects observed in that study were already manifest within the first week after infarction (39), suggests that the salutary effect of FG-0041 was because of HIF stabilization rather than prevention of fibrosis." (p. 13464, lines 5 to 13 of right column)

2 Evidence A No. 14

(1) Title of invention

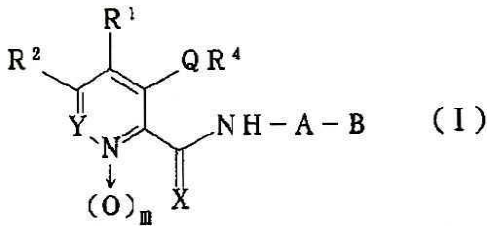
"Substituted heterocyclic carboxyamides, their preparation and their use as pharmaceuticals"

(2) The scope of claims

A [Claim 1]

"A compound of following formula (I):

[Chemical 1]



[wherein, ...], and a physiologically active salt thereof (except 3-hydroxypyridine-2-carboxylic acid-N-(carboxymethyl)amide."

B [Claim 12]

"The compound according to any of claims 1 to 8, wherein the compound is used for producing a pharmaceutical against fibrotic disease."

(3) The detailed description of the invention

A " N-Oxalylglycines which are inhibitors of prolyl-4-hydroxylase are disclosed in J. Med. Chem. 1992, 35, 2652 to 2658 (Cunliffe et al.), and EP-A-0457163 (Baader et al.). 3-Hydroxypyridine-2-carboxylic acid N-(carboxymethyl)amide is disclosed in G. Yolles et al., Bull. Soc. Chim. Fr. 1965, 8, 2252 to 2259. Hydroxyisoquinolinecarboxylic acid glycylamides and hydroxyquinolinecarboxylic acid glycylamides are disclosed in Biochem. Soc. Trans. 1991, 19, 812 to 815 (Franklin et al.). It has surprisingly now been found that heterocylic carboxamides having an OH or SH function in the ortho-position to the amide function are highly effective inhibitors of prolyl-4-hydroxylase." (paragraph [0004])

B "Compounds of the formula I are preferred in the highest degree in which Q is O, X is O, Y is CR^3, m is 0, A is a $-CH_2-$ group, B is $-CO_2H$, R^1 is hydrogen, (C_1-C_{10})-alkoxy, (C_5-C_6)-cycloalkyloxy, (C_5-C_6)-cycloalkyl-(C_1-C_2)-alkoxy, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, ($C_1$-$C_4$)-alkoxy-($C_1$-$C_4$)-alkoxy, substituted phenoxy or substituted benzyloxy, where the phenyl radical is substituted by a substituent from the group fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy, and R^2, R^3 and R^4 are hydrogen, including their physiologically active salts." (paragraph [0012])

C "The invention relates to the use of compounds of the formula I, and also the physiologically tolerated salts, for inhibiting collagen biosynthesis. The invention relates to the use of compounds of the formula I, and also the physiologically tolerated salts, for inhibiting prolyl-4-hydroxylase." (paragraph [0015])

3 Evidence A No. 15

(1) Title of invention

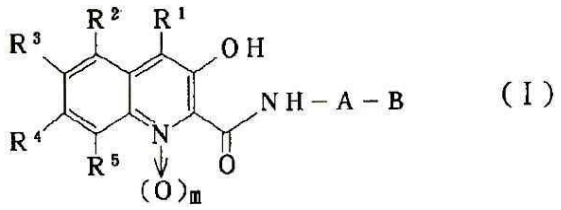
"Substituted quinoline-2-carboxamides, their preparation and their use as pharmaceuticals, and intermediates"

(2) The scope of claims

A [Claim 1]

"A compound of formula (I)

[Chemical 1]



(I)

[wherein, ...] or a physiologically active salt thereof."

B [Claim 25]

"The compound according to any of claims 1 to 19, wherein the compound is used for producing a pharmaceutical against fibrotic disease."

(3) The detailed description of the invention

A "Prodrugs of pyridine-2,4(5)-dicarboxylates are also known. These are described in EP-A-0590520 and EP-A-0562512. N-Oxalylglycines as inhibitors of prolyl 4-hydroxylase are known from J. Med. Chem. 1992, 35, 2652 to 2658 (Cunliffe et al.), and EP-A-0457163 (Baader et al.). 3-Hydroxypyridine-2-carboxylic acid N-(carboxymethyl)-amide is known from G. Yolles et al., Bull. Soc. Chim. Fr. 1965, 8, 2252 to 2259. Hydroxyisoquinoline- and hydroxycinnolinecarboxylic acid glycylamides are known from Biochem. Soc. Trans. 1991, 19, 812 to 815 (Franklin et al.). EP-A-0661269 discloses substituted heterocyclic carboxylic acid amides and their use as inhibitors of prolyl 4-hydroxylase and as inhibitors of collagen biosynthesis.

The object was to search for even more active inhibitors of prolyl hydroxylase and for other inhibitors of collagen biosynthesis. It has now been found that a selection of the compounds included in EP-A-0661269; that is to say, the quinoline-2-carboxylic acid amides having an OH function in the ortho position relative to the amide function, show a surprisingly high inhibition of prolyl 4-hydroxylase in cell cultures."

(paragraphs [0003] to [0004])

B "Especially preferred compounds of the formula I are those in which m is 0, A is a -CH_2- group, B is -CO_2H, R^1 and R^5 are hydrogen, and R^2, R^3 and R^4 are identical or different and are hydrogen, (C_1-C_{18})-alkyl, (C_1-C_{18})-alkenyl, phenyl, chlorine, fluorine, bromine, trifluoromethyl, (C_1-C_{18})-alkylsulfinyl, (C_1-C_{18})-alkylsulfonyl, phenylsulfinyl, phenylsulfonyl, naphthylsulfinyl, naphthylsulfonyl, (C_1-C_{18})-alkoxy, (C_3-C_8)-cycloalkoxy, (C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, -O-$[CH_2]_x$-$C_fH_{(2f+1-g)}F_g$, phenyl-(C_1-C_4)-alkoxy, phenoxy, (C_1-C_{12})-alkanoyl, phenyl-(C_1-C_4)-alkanoyl or benzoyl, where, in substituents with a phenyl or naphthyl ring, this optionally carries up to 5 identical or different substituents from the series comprising fluorine, chlorine, bromine, nitrile, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, -O-$[CH_2]_x$-$C_fH_{(2f+1-g)}F_g$, and (C_1-C_6)-alkylsulfonyl, including their physiologically active salts." (paragraph [0019])

C "The invention relates to the use of compounds of the formula I and the physiologically tolerated salts for inhibition of collagen biosynthesis. The invention relates to the use of compounds of the general formula I and their physiologically tolerated salts for inhibition of prolyl 4-hydroxylase. The invention furthermore relates to the use of compounds of the formula I and their physiologically tolerated salts for the preparation of a pharmaceutical (medicament) against fibrotic diseases." (paragraph [0029])

4 Evidence A No. 16

(1) Title of invention

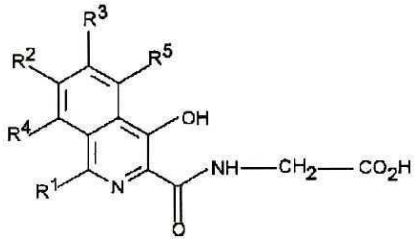
"Substituted isoquinoline-3-carboxamides, their preparation and their use as pharmaceuticals"

(2) The scope of claims

A [Claim 1]

"A compound of formula (I)

[Chemical 1]



(I)

[wherein, ...] or a physiologically active salt thereof."

B [Claim 23]

"The compound according to any of claims 1 to 17, wherein the compound is used for producing a pharmaceutical against fibrotic disease."

(3) The detailed description of the invention

A "Prodrugs of pyridine-2,4(5)-dicarboxylates are also known. These are described in EP-A-0590520 and EP-A-0562512. N-Oxalylglycines as inhibitors of prolyl-4-hydroxylase are known from Cunliffe et al., J. Med. Chem. 35 (1992) 2652-2658, and EP-A-0457163 (Baader et al.). 3-Hydroxypyridine-2-carboxylic acid N-(carboxymethyl)amide is known from G. Yolles et al., Bull. Soc. Chim. Fr. 8 (1965) 2252-2259. N-((4-Hydroxyisoquinolin-3-yl)carbonyl)glycine and N-((7-bromo-4-hydroxyisoquinolin-3-yl)carbonyl)glycine are known from Franklin et al., Biochem. Soc. Trans. 19 (1991) 812-815, the in-vivo activity on collagen biosynthesis being poor in the case of N-((4-hydroxyisoquinolin-3-yl)carbonyl)glycine. Hydroxyquinolinecarboxylic acid glycylamides are also disclosed here. In T. J. Franklin, "Therapeutic Approaches to Organ Fibrosis", INT. J. Biochem. Cell. Biol., 29(1) (1997) 79-89, a toxic action on the liver (steatosis) in rats is reported in the case of N-((7-bromo-4-hydroxyisoquinolin-3-yl)carbonyl)glycine in addition to the in-vivo inhibition of collagen biosynthesis. EP-A-0661269 discloses substituted heterocyclic carboxamides and their use as inhibitors of prolyl-4-hydroxylase and as inhibitors of collagen biosynthesis.

The object of the present invention was to search for more highly active inhibitors of prolyl hydroxylase. The object was furthermore to search for active inhibitors of prolyl hydroxylase which do not cause steatosis. It has now been found that novel isoquinoline-3-carboxamides are surprisingly strong prolyl-4-hydroxylase inhibitors which do not cause steatosis." (paragraphs [0003] to [0004])

B "Particularly preferred compounds of the formula I are those in which R^1 is hydrogen

or chlorine, R^2 is (C_1-C_8)-alkoxy, chlorine, or benzyloxy, and R^3, R^4 and R^5 are hydrogen; or in which R^1 is hydrogen or chlorine, R^2 is hydrogen or chlorine, R^3 is (C_1-C_8)- alkoxy, chlorine, or benzyloxy; and R^4 and R^5 are hydrogen; or in which R^1 is hydrogen or chlorine, R^2 and R^3 are hydrogen or chlorine, R^4 is (C_1-C_6)-alkoxy, chlorine, or benzyloxy, and R^5 is hydrogen." (paragraph [0008])

C "The invention relates to the use of compounds of the formula I and the physiologically tolerable salts for the inhibition of collagen biosynthesis. The invention relates to the use of compounds of the formula I and the physiologically tolerable salts for the inhibition of prolyl-4-hydroxylase. The invention furthermore relates to the use of compounds of the formula I and the physiologically tolerable salts for the production of a pharmaceutical against fibrotic disorders. The invention furthermore relates to the use of compounds of the formula I and the physiologically tolerable salts for the production of a pharmaceutical against fibrotic disorders of the liver, the kidney, the lungs, and the skin." (paragraph [0018])

5 Evidence A No. 7

(1) Title

"Perspectives on Oxygen Sensing"

(2) Physiological Perspective

"A universal response to reduced O_2 availability involves the expression of hypoxia-inducible factor 1 (HIF-1), a transcriptional activator of genes encoding erythropoietin (EPO), which stimulates red blood cell production, and vascular endothelial growth factor, which stimulates angiogenesis." (p. 281, lines 22 to 28 below authors of left column)

(3) Medical Perspective

"Not only does hypoxia represent a fundamental physiologic response in all organisms, but hypoxia is also critical to the pathogenesis of major causes of mortality, including myocardial ischemia, stroke, cancer, and chronic lung disease. Although these issues are beyond the scope of the present discussion, genetic and pharmacologic strategies designed to amplify adaptive responses to hypoxia in ischemic tissues and to inhibit these responses in cancer cells hold great promise as novel and effective therapies for these fatal disorders." (p. 281, lines 38 to 47 below authors of left column)

6 Evidence A No. 8

(1) Title

"Erythropoietin -up to date-"

(2) Abstract

"Erythropoietin (EPO) is a glycoprotein hormone for modulating production of erythrocytes. EPO is subjected to modulation with a positive or negative transcription factor through an oxygen sensor. Especially, HIF-1 positively controls expression of EPO gene, and negatively controls GATA. It is thought that L-NMMA increased in renal anemia increases binding activity of GATA and GATA mRNA, the activity of EPO promoter is reduced, and EPO is reduced, thereby developing anemia." (p. 539, lines 1 to 5)

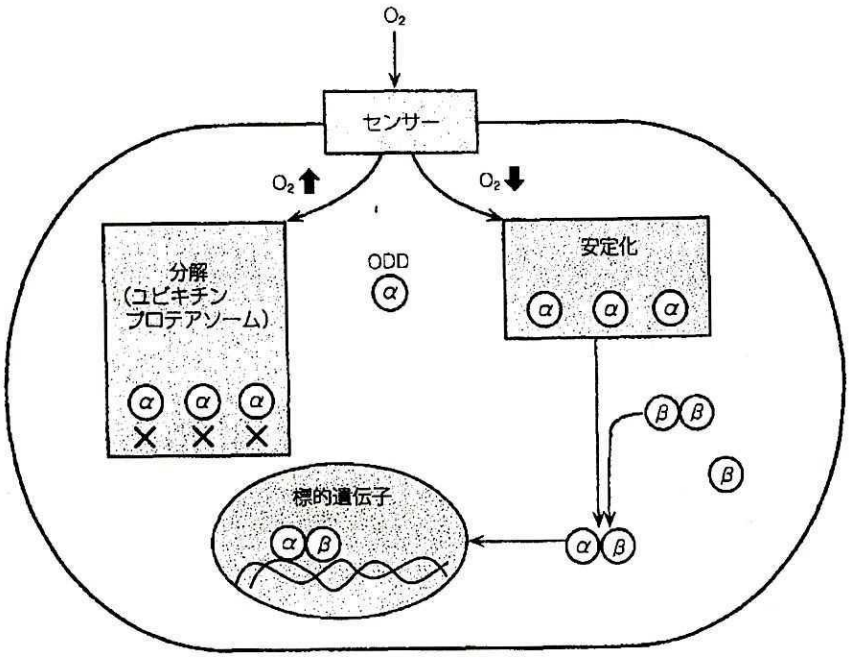
(3) Introduction

"Erythropoietin (EPO) is a glycoprotein hormone for modulating production of erythrocytes. EPO acts on BFU-E, CFU-E which are erythroid progenitors, and through binding EPO with EPO receptor (EPOR) in these cells, erythroid differentiation is enhanced by intracellular signaling. Generally, it has been known that erythrocytosis is developed by being exposed to low oxygen level such as on a high mountain or administering cobalt, and it is thought that an oxygen sensor is activated by the stimulation, activates a transcription factor through pathways, and EPO protein is increased for enhancing expression of EPO gene, thereby developing erythrocytosis." (p. 539, lines 2 to 12 of left column)

(4) "4. Expression of EPO gene is modulated by positive or negative transcription factor", "2) HIF-1"

"As an ODD domain is generally degraded by ubiquitin/proteasome in the atmosphere, the HIF-1α chain cannot form a heterodimer with a constitutively expressed HIF-1β chain. However, as degradation with ubiquitin/proteasome is not caused in low oxygen level, expression of the HIF-1α chain is caused and the HIF-1α chain forms a heterodimer with the HIF-1β chain. It is thought that this HIF-1 moves into a nucleus, and binds to HIF-1 binding sites of EPO, VEGF, TH, LDH, thereby inducing expression of each gene [17]. (FIG. 2)." (p. 542, lines 27 to 36 of left column)

(5) Figure 2 (p. 543)



センサー sensor

分解（ユビキチンプロテアソーム） degradation (ubiquitin/proteasome)

安定化 stabilization

標的遺伝子 target gene

"FIG. 2 Oxygen sensor, and α and β chains of HIF-1

ODD: oxygen dependent degradation"

(6) "5. Increasing L-NMMA causes renal anemia"

"In addition, we analyzed whether inhibiting production of EPO caused by increasing L-NMMA is released by administering L-arginine, using Hep3B cells and mice. The result shows that reducing production of NOcGMP and inhibiting production of EPO caused by increasing L-NMMA was improved by administering L-arginine. Therefore, it was proved that administration of L-arginine is worth trying for use as a novel treatment for renal anemia[21)]." (p. 543, lines 1 to 8 of right column)

7 Evidence A No. 9

(1) Title

"Epolones induce erythropoietin expression via hypoxia-inducible factor-1α activation"

(2) Abstract

"Induction of erythropoietin (Epo) expression under hypoxic conditions is mediated by the heterodimeric hypoxia-inducible factor (HIF)-1. Following binding to the 3' hypoxia-response element (HRE) of the Epo gene, HIF-1 markedly enhances Epo transcription. ... Epolones are fungal products known to induce Epo expression in hepatoma cells. We found that epolones (optimal concentration 4-8 μmol/L) potently induce HIF-1α protein accumulation and nuclear translocation as well as HIF-1 DNA binding and reporter gene transactivation." (p. 1558, line 1 of left column to line 7 of center column)

(3) Introduction

"The glycoprotein hormone erythropoietin (Epo), produced by the embryonic liver and the adult kidney, is the main stimulator of erythropoiesis.[1] Recombinant Epo is widely used to treat patients suffering from anemia. However, recombinant Epo is expensive and must be administered intravenously or subcutaneously. Thus, an orally active, small molecular weight compound that induces endogenous Epo production would be an alternative for the treatment of anemia not caused by deficient renal Epo production. ... Hereinafter, we refer to this class of substances, capable of inducing Epo expression, as "epolones." The mechanism of Epo induction via epolones and the involved *cis*-regulatory elements, however, have remained unidentified." (p. 1558, lines 1 to 20 of left column)

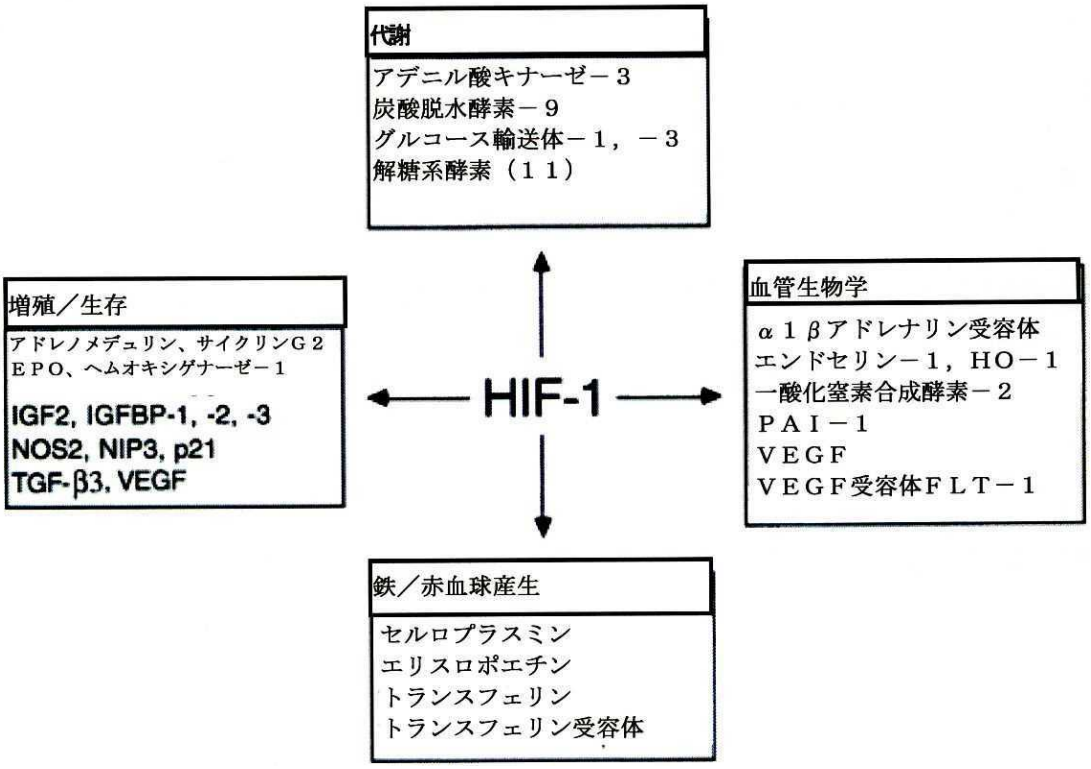
8 Evidence A No. 11

(1) Title

"HIF-1, O_2, and the 3 PHDs: How Animal Cells Signal Hypoxia to the Nucleus"

(2) "HIF-1"

A Figure 1 (p. 2)



代謝 Metabolism

アデニル酸キナーゼ－３ Adenylate kinase-3

炭酸脱水酵素－９ Carbonic Anhydrase-9

グルコース輸送体－１，－３ Glucose Transporter-1, -3

解糖系酵素（１１） Glycolytic Enzymes (11)

増殖／生存 Proliferation/Survival

アドレノメデユリン、サイクリンＧ２ＥＰＯ、ヘムオキシゲナーザー１

Adrenomedulin, Cyclin G2, EPO, Heme oxygenase-1

血管生物学 Vascular Biology

α１βアドレナリン受容体エンドセリン－１，ＨＯ－１一酸化窒素合成酵素－２

α1β Adrenergic Receptor, Endothelin-1, HO-1, Nitric Oxide Synthase-2

ＶＥＧＦ受容体ＦＬＴ－１ VEGF receptor FLT-1

鉄／赤血球産生 Iron/Erythropoiesis

セルロプラスミン Ceruloplasmin

エリスロポエチン Erythropoietin

トランスフェリン Transferrin

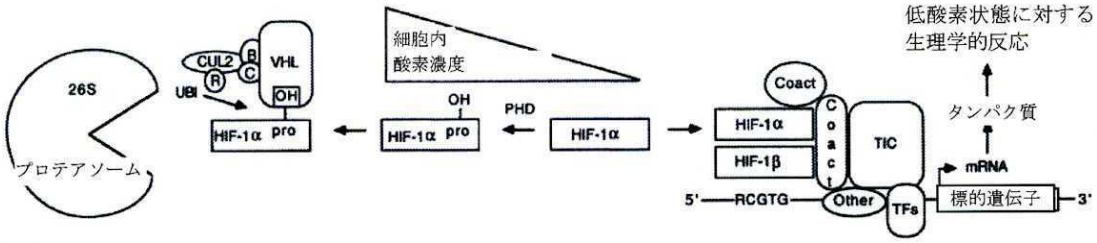
トランスヌフェリン受容体 Transferrin Receptor

"FIG. 1 Representative HIF-1 Target Genes and Their Roles in Oxygen Homeostasis

HIF-1-regulated genes include the 11 glycolytic enzymes aldolase A, aldolase C, enolase 1, glyceraldehyde-3-phosphate dehydrogenase, hexokinase 1, hexokinase 2, lactate dehydrogenase A, phosphofructokinase L, phosphoglycerate kinase 1, pyruvate kinase M, and triosephosphate isomerase. Abbreviations: ...; HO, heme oxygenase; IGF, insulin-like growth factor; IGFBP, IGF binding protein; NOS, nitric oxide synthase; PAI, plasminogen activator inhibitor; TGF, transforming growth factor; VEGF, vascular endothelial growth factor."

(3) "VHL"

A Figure 2 (p. 2)



プロテアソーム proteasome

細胞内酸素濃度 Cellular Oxygen Concentration

低酸素状態に対する生理学的反応 Physiologic Response to Hypoxia

タンパク質 Protein

標的遺伝子 Target Gene

"FIG. 2 Regulation of HIF-1α Expression by Cellular O_2 Concentration

O_2 availability determines the rate at which HIF-1α is subject to prolyl hydroxylation by PHDs 1-3. Prolyl hydroxylation is required for the interaction of HIF-1α with VHL, which recruits elongins B and C, Cullin 2 (CUL2), and RBX1 (R) to constitute a functional E3 ubiquitin-protein ligase complex. Ubiquitination of HIF-1α targets the protein for degradation by the 26S proteasome. Under hypoxic conditions, HIF-1β dimerizes with HIF-1α, which escapes prolyl hydroxylation, ubiquitination, and degradation. The HIF-1 heterodimer binds to hypoxia response elements containing the core recognition sequence 5'-RCGTG-3' and recruits coactivator (Coact) molecules, resulting in increased transcription initiation complex (TIC) formation and mRNA synthesis, which ultimately results in the production of proteins that mediate physiologic responses to hypoxia. The battery of HIF-1 target genes that are expressed in response to hypoxia are cell-type-specific and are determined by the binding of other transcription factors (TFs) which establish basal rates of transcription."

(4) "Clinical relevance"

"Hypoxia plays an important role in the pathophysiology of ischemic cardiovascular disease, cancer, stroke, and chronic lung disease, which are the most common causes of mortality in the U.S. population. There is a growing body of data indicating that HIF-1 contributes to the pathogenesis of cancer and hypoxic pulmonary hypertension while protecting against the ischemia and infarction (reviewed in Semenza, 2000). Whether targeting HIF-1 for inhibition (in cancer and lung disease) or induction (in ischemic disorders) will be of therapeutic utility remains to be established." (p. 3, lines 7 to 17 of right column)

9 Evidence A No. 17

(1) Title

"HIFα Targeted for VHL-Mediated Destruction by Proline Hydroxylation: Implications for O_2 Sensing"

(2) Abstract

"HIF (hypoxia-inducible factor) is a transcription factor that plays a pivotal role in cellular adaptation to changes in oxygen availability. In the presence of oxygen, HIF is

targeted for destruction by an E3 ubiquitin ligase containing the von Hippel-Lindau tumor suppressor protein (pVHL). We found that human pVHL binds to a short HIF-derived peptide when a conserved proline residue at the core of this peptide is hydroxylated. Because proline hydroxylation requires molecular oxygen and Fe^{2+}, this protein modification may play a key role in mammalian oxygen sensing." (p. 464, lines 1 to 8 below authors)

(3) Introduction

"How cells sense changes in ambient oxygen is a central question in biology. In mammalian cells, lack of oxygen, or hypoxia, leads to the stabilization of a sequence-specific DNA binding transcription factor called HIF, which transcriptionally activates a variety of genes linked to processes such as angiogenesis and glucose metabolism (1-4). HIF binds to DNA as a heterodimer consisting of an α subunit and a β subunit.

Von Hippel-Lindau (VHL) disease is a hereditary cancer syndrome characterized by the development of highly vascular tumors that overproduce hypoxia-inducible mRNAs such as vascular endothelial growth factor (VEGF) (5). The product of the VHL tumor suppressor gene, pVHL, is a component of a multiprotein complex that bears structural and functional similarity to SCF (Skp1/Cdc53 or Cullin/F-box) ubiquitin ligases (6-11). In the presence of oxygen, pVHL, in association with elongin B and elongin C, binds directly to HIFα subunits and targets them for polyubiquitination and destruction (7-10). Cells lacking functional pVHL cannot degrade HIF and thus overproduce mRNAs encoded by HIF target genes (12)." (p. 464, line 1 of left column to line 2 of center column)

(4) Discussion

A "The vertebrate type I and type II prolyl-4-hydroxylases are tetramers consisting of two α subunits [α(I) and α(II), respectively] and two common β subunits (22). These enzymes require Fe^{2+}, molecular oxygen, 2-oxoglutarate, and ascorbate and act upon collagen and other proteins that contain collagen-line sequences. The pVHL binding peptide present in HIF does not closely resemble the naturally occurring or synthetic prolyl hydroxylation targets identified to date. Moreover, HIF is intracellular, whereas the majority of proline hydroxylase activity is associated with the endoplasmic reticulum, where it is required for normal collagen biosynthesis. It is therefore unlikely

that HIF is modified by the type I and type II prolyl 4-hydoxylases." (p. 467, lines 1 to 17 of center column)

B "Several small-molecule proline hydroxylase inhibitors have been developed as antifibrotic agents and can now be tested in ischemia models (22, 32-34)." (p. 467, lines 40 to 44 of center column)

10 Evidence A No. 18

(1) Title

"Targeting of HIF-1α to the von Hippel-Lindau Ubiquitylation Complex by O_2-Regulated Prolyl Hydroxylation"

(2) Abstract

"Hypoxia-inducible factor (HIF) is a transcriptional complex that plays a central role in the regulation of gene expression by oxygen. In oxygenated and iron replete cells, HIF-α subunits are rapidly destroyed by a mechanism that involves ubiquitylation by the von Hippel-Lindau tumor suppressor (pVHL) E3 ligase complex. This process is suppressed by hypoxia and iron chelation, allowing transcriptional activation. Here we show that the interaction between human pVHL and a specific domain of the HIF-1α subunit is regulated through hydroxylation of a proline residue (HIF-1α P564) by an enzyme we have termed HIF-α prolyl-hydroxylase (HIF-PH). An absolute requirement for dioxygen as a cosubstrate and iron as cofactor suggests that HIF-PH functions directly as a cellular oxygen sensor." (p. 468, lines 1 to 11 below authors)

(3) Introduction

"HIF is a key regulator of responses to hypoxia, occupying a central position in oxygen homeostasis in a wide range of organisms (1). Among its transcriptional targets are genes with critical roles in angiogenesis, erythropoiesis, energy metabolism, vasomotor function, and apoptotic/proliferative responses. HIF is essential for normal development (2) and plays a key role in pathophysiological responses to ischemia/hypoxia as well as in tumor growth and angiogenesis (1). The HIF DNA binding complex is a heterodimer of α and β subunits (3). In oxygenated cells, the α subunits are unstable, being targeted for proteasomal destruction by specific degradation domains (4-7). This process is dependent on the von Hippel-Lindau tumor suppressor

(pVHL) (8), which serves as the recognition component of a ubiquitin ligase (9, 10) that promotes ubiquitin-dependent proteolysis of HIF-α (11-14). In hypoxic cells, HIF-α degradation is suppressed, leading to transcriptional activation of target genes." (p. 468, line 1 of left column to line 6 of center column)

(4) "Prolyl hydroxylation of a HIF-1α degradation domain"

A "We next tested a series of 2-oxoglutarate analogs that act as competitive inhibitors of PHs (31) for their ability to inhibit HIF-PH. Complete inhibition of modifying activity was observed with N-oxalylglycine." (p. 471, lines 7 to 12 of left column)

B "In mammalian cells, the best characterized prolyl-4-hydroxylases are the α_1 and α_2 isoforms that modify collagen. These enzymes are reported to have a strict substrate specificity for prolyl residues in collagen repeat sequences, typically $(Pro\text{-}Pro\text{-}Gly)_n$ (28). When tested as substrate for recombinant (α_1 or α_2) human prolyl-4-hydroxylase, the HIF showed no activity (35). We therefore postulate that HIF-PH is a previously unknown prolyl-4-hydroxylase." (p. 471, lines 1 to 11 of center column)

11 Evidence A No. 27

(1) Title

"Role of HIF-1 as a transcription factor involved in embryonic development, cancer progression, and apoptosis (review)."

(2) "Abstract"

"It (Note by the body: HIF-1) also regulates the expression of the angiogenic factor VEGF and stimulates erythropoiesis via EPO production. HIF-1 is a protein necessary for the normal embryonic and cardiovascular system development, but seems to be also involved in cancer progression and apoptosis. Thus, it appears that HIF-1 plays a central role in normal cellular functions and in tissue metabolism, but it is also involved in pathological evolutions, raising its interest as a therapeutic target. In this review, we summarize the dual role of HIF-1 as a major component of embryo development, as well as an element of tumor progression and of anoxia-induced apoptosis." (p. 253, lines 5 to 16 of left column)

(3) "6. Conclusion"

"It is thought that HIF-1 or a pathway for activating HIF-1 is a new target for

treating various diseases such as cancer, local ischemia, thrombosis, and anemia. As a therapeutic approach, introduction of suicide gene controlled by HRE element in solid tumor is thought of (40). Further, using a gene treatment approach, delivery of erythropoietin can be controlled by using an EPO expression vector under control of HRE (41). However, further study is needed to understand the double role of HIF-1; that is to say, not only a role as a factor required for surviving in development and low oxygen level, but also a role as protein enhancing apoptosis under anaerobic conditions in which progress of tumor is enhanced." (p. 258, lines 8 to 20 of left column)

No. 6 Judgment by the body

First we will examine the Reason 2 for invalidation, and then will examine other reasons for invalidation.

1 Reason 2 for invalidation

(1) Regarding Corrected invention 1

A Invention described in Evidence A No. 14

In claim 1 in Evidence A No. 14, a compound represented by formula I (Note by the body: The chemical formula of formula I is indicated in No. 5 2(2)A above; hereinafter, indication of the chemical formula is omitted.) is described (No. 5 2(2)A above). In paragraph [0012], it is described that "Compounds of the formula I are preferred in the highest degree in which Q is O, X is O, Y is CR^3, m is 0, A is a $-CH_2-$ group, B is $-CO_2H$, R^1 is hydrogen, (C_1-C_{10})-alkoxy, ... , $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, ... , substituted phenoxy, or substituted benzyloxy, where the phenyl radical is substituted by a substituent from the group fluorine, chlorine, cyano, ... , (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy, and R^2, R^3 and R^4 are hydrogen" (No. 5 2(3)B above). Further, in claim 12, the compound according to claim 1, wherein the compound is used for producing a pharmaceutical against fibrotic disease, is described (No. 5 2(2)B above), and the compound has action for inhibiting prolyl-4-hydroxylase (No. 5 2(3)C above). Thus, it is recognized that, in Evidence A No. 14, the invention of use of a compound represented by formula I, used for producing a pharmaceutical against fibrotic disease, [wherein Q is O, X is O, Y is CR^3, m is 0, A is a $-CH_2-$ group, B is $-CO_2H$, R^1 is hydrogen, (C_1-C_{10})-alkoxy, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, substituted phenoxy, or substituted benzyloxy, where the phenyl radical is substituted by a substituent from the group

fluorine, chlorine, cyano, (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy, and R^2, R^3 and R^4 are hydrogen], in which the compound has action for inhibiting prolyl-4-hydroxylase, is described. (Hereinafter, this invention may be referred to as the "Evidence A No. 14 invention".)

B Invention described in Evidence A No. 15

In claim 1 in Evidence A No. 15, a compound represented by formula (I) (Note by the body: The chemical formula of formula (I) is indicated in No. 5 3(2)A above; hereinafter, indication of the chemical formula is omitted) is described (No. 5 3(2)A above). In paragraph [0019], it is described that "Especially preferred compounds of the formula I are those in which m is 0, A is a -CH_2- group, B is -CO_2H, R^1 and R^5 are hydrogen, and R^2, R^3 and R^4 are identical or different and are hydrogen, (C_1-C_{18})-alkyl, ... , phenyl, chlorine, fluorine, bromine, ... , (C_1-C_{18})-alkoxy, ... , -O-$[CH_2]_x$-$C_fH_{(2f+1-g)}F_g$, phenyl-(C_1-C_4)-alkoxy, phenoxy, ... , where, in substituents with a phenyl ... ring, this optionally carries up to 5 identical or different substituents from the series comprising fluorine, chlorine, bromine, nitrile, ... , (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, ..." (No. 5 3(3)B above). Further, in claim 25, the compound according to claim 1, wherein the compound is used for producing a pharmaceutical against fibrotic disease, is described (No. 5 3(2)B above), and the compound has action for inhibiting prolyl-4-hydroxylase (No. 5 3(3)C above). Thus, it is recognized that, in Evidence A No. 15, the invention of use of a compound represented by formula (I), used for producing a pharmaceutical against fibrotic disease, [wherein m is 0, A is a -CH_2- group, B is -CO_2H, R^1, R^2 and R^5 are hydrogen, and R^3 and R^4 are identical or different and are hydrogen, (C_1-C_{18})-alkyl, phenyl, chlorine, fluorine, bromine, (C_1-C_{18})-alkoxy, -O-$[CH_2]_x$-$C_fH_{(2f+1-g)}F_g$, phenyl-(C_1-C_4)-alkoxy or phenoxy, where, in substituents with a phenyl ring, this optionally carries up to 5 identical or different substituents from the series comprising fluorine, chlorine, bromine, nitrile, (C_1-C_6)-alkyl and (C_1-C_6)-alkoxy, in which the compound has action for inhibiting prolyl-4-hydroxylase, is described. (Hereinafter, this invention may be referred to as the "Evidence A No. 15 invention".)

C Invention described in Evidence A No. 16

In claim 1 in Evidence A No. 16, a compound represented by formula I (Note by the body: The chemical formula of formula I is indicated in No. 5 4(2)A above; hereinafter, indication of the chemical formula is omitted) is described (No. 5 4(2)A

above). In paragraph [0008], it is described that "Particularly preferred compounds of the formula I are those in which R^1 is hydrogen or chlorine, R^2 is (C_1-C_8)-alkoxy, chlorine, or benzyloxy, and R^3, R^4 and R^5 are hydrogen; or in which R^1 is hydrogen or chlorine, R^2 is hydrogen or chlorine, R^3 is (C_1-C_8)- alkoxy, chlorine, or benzyloxy; and R^4 and R^5 are hydrogen ..." (No. 5 4(3)B above). Further, in claim 23, the compound according to claim 1, wherein the compound is used for producing a pharmaceutical against fibrotic disease, is described (No. 5 4(2)B above), and the compound has action for inhibiting prolyl-4-hydroxylase (No. 5 4(3)C above). Thus, it is recognized that, in Evidence A No. 16, the invention of use of a compound represented by formula I, used for producing a pharmaceutical against fibrotic disease, [wherein R^1 is hydrogen or chlorine, R^2 is (C_1-C_8)-alkoxy, chlorine, or benzyloxy, and R^3, R^4 and R^5 are hydrogen; or in which R^1 is hydrogen or chlorine, R^2 is hydrogen or chlorine, R^3 is (C_1-C_8)- alkoxy, chlorine, or benzyloxy; and R^4 and R^5 are hydrogen], in which the compound has action for inhibiting prolyl-4-hydroxylase, is described. (Hereinafter, this invention may be referred to as the "Evidence A No. 16 invention".)

D Comparison

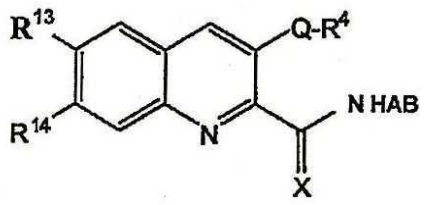
(a) Comparison of Corrected invention 1 with invention described in Evidence A No. 14

As in formula (I) of the Corrected invention 1, x is O, A is -CH_2-, and B is -CO_2H, heterocyclic carboxamide compounds specified by formula (I) of the Corrected invention 1 include a compound having a "-C(=O)-NH-CH_2-CO_2H group" as a substituent of heterocycle. On the other hand, in a compound represented by formula I in the Evidence A No. 14 invention, X is O, A is a -CH_2- group, and B is CO_2H, so the compound has a "-C(=O)-NH-CH_2-CO_2H group" in a pyridine ring as a substituent. Thus, both inventions correspond in use of a heterocyclic compound having a substituent of a "-C(=O)-NH-CH_2-CO_2H group", for producing a pharmaceutical. However, the two inventions are different in that the heterocycle in the Corrected invention 1 is quinoline (a compound represented by formula (Ia)) or isoquinoline (a compound represented by formula (Ib)); on the other hand, the heterocycle in the Evidence A No. 14 invention is pyridine (difference feature 14-1). Further, the two inventions are different in that use of the pharmaceutical in the Corrected invention 1 is to treat anemia and the heterocyclic compound inhibits HIF prolyl hydroxylase; on the other hand, use of the pharmaceutical in Evidence A No. 14 invention is against fibrotic

disease and the heterocyclic compound has action for inhibiting prolyl-4-hydroxylase (difference feature 14-2).

(b) Comparison of Corrected invention 1 with invention described in Evidence A No. 15

Comparing the Corrected invention 1 with the Evidence A No. 15 invention, both inventions correspond in use of a compound represented by general formula 15-Ia

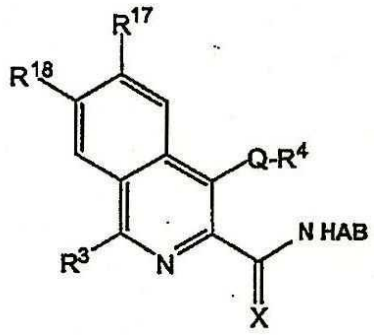


[wherein, X is O, A is a -CH_2 group, B is -CO_2H, R^{13} and R^{14} are identical or different and are hydrogen, (C_1-C_{18})-alkyl, phenyl, chlorine, fluorine, bromine, (C_1-C_{18})-alkoxy, phenyl-(C_1-C_4)-alkoxy or phenoxy, where, in substituents with a phenyl ring, this optionally carries up to 5 identical or different substituents from the series comprising fluorine, chlorine, bromine, nitrile, (C_2-C_6)-alkyl and (C_1-C_6)-alkoxy.], for producing a pharmaceutical.

However, the two inventions are different in that use of the pharmaceutical in the Corrected invention 1 is to treat anemia and the compound represented by general formula 15-Ia inhibits HIF prolyl hydroxylase; on the other hand, use of the pharmaceutical in the Evidence A No. 15 invention is against fibrotic disease and the compound represented by general formula 15-Ia has action for inhibiting prolyl-4-hydroxylase (difference feature 15-2).

(c) Comparison of Corrected invention 1 with invention described in Evidence A No. 16

Comparing the Corrected invention 1 with the Evidence A No. 16 invention, both inventions are common in use of a compound represented by general formula 16-Ib



[wherein, R^3 is hydrogen or chlorine, R^{18} is (C_1-C_8)-alkoxy, chlorine or benzyloxy, R^{17} is hydrogen; or, R^3 is hydrogen or chlorine, R^{18} is hydrogen or chlorine, R^{17} is (C_1-C_8)-alkoxy, chlorine or benzyloxy.], for producing a pharmaceutical. However, the two inventions are different in that use of the pharmaceutical in the Corrected invention 1 is to treat anemia and the compound represented by general formula 16-Ib inhibits HIF prolyl hydroxylase; on the other hand, use of the pharmaceutical in the Evidence A No. 16 invention is against fibrotic disease and the compound represented by general formula 16-Ib has action for inhibiting prolyl-4-hydroxylase (difference feature 16-2).

E Judgment

As described in D above, the Corrected invention 1, and the Evidence A No. 14 invention, the Evidence A No. 15 invention and the Evidence A No. 16 invention are different in difference features 14-2, 15-2, and 16-2, respectively. These difference features are that in the Corrected invention 1, use of a pharmaceutical is for treating anemia and an active ingredient inhibits HIF prolyl hydroxylase; on the other hand, in the Evidence A No. 14 invention to Evidence A No. 16 invention, use of a pharmaceutical is for treating fibrotic disease and an active ingredient has action for inhibiting prolyl-4-hydroxylase. We will examine these difference features below.

As the Evidence A No. 14 invention to the Evidence A No. 16 invention inhibit collagen biosynthesis (No.5 2(3)C, 3(3)C and 4(3)C above), it is understood that prolyl-4-hydroxylase in the Evidence A No. 14 invention to the Evidence A No. 16 invention is prolyl-4-hydroxylase involved in biosynthesis and modification of collagen, and this is recognized as "type I or type II prolyl-4-hydroxylase" in Evidence A No. 17 (No. 5 9(4)A above) and "(α1 or α2) human prolyl-4-hydroxylase" in Evidence A No. 18 (No. 5 10(4)B above). In Evidence A No. 17, it is described that "The pVHL binding peptide

present in HIF does not closely resemble the naturally occurring or synthetic prolyl hydroxylation targets identified to date. Moreover, HIF is intracellular, whereas the majority of proline hydroxylase activity is associated with the endoplasmic reticulum where it is required for normal collagen biosynthesis. It is therefore unlikely that HIF is modified by the type I and type II prolyl 4-hydoxylases." (No. 5 9(4)A above), it is also described that there is low possibility of hydroxylation of a proline residue in HIF with prolyl-4-hydroxylase described in Evidence A No. 14 to A No. 16. Further, it is described in Evidence A No. 18 that "When tested as a substrate for recombinant (α_1 or α_2) human prolyl-4-hydroxylase, the HIF showed no activity (35). We therefore postulate that HIF-PH is a previously unknown prolyl-4-hydroxylase." (No. 5 10(4)B), and it is also described that prolyl-4-hydroxylase described in Evidence A No. 14 to A No. 16 does not perform prolyl hydroxylation of HIF and it is assumed that the prolyl-4-hydroxylase and HIF-PH are different. In Evidence A No. 6, which was well-known between filing date as a basis of claiming priority and original filing date of the Patent, it is described that HIF prolyl hydroxylase and I type or II type prolyl-4-hydroxylase modifying collagen, described in Evidence A No. 14 to A No. 16, are different (No. 5 1(3) above).

As described, before the original filing date of the Patent, it is generally thought that prolyl-4-hydroxylase described in the Evidence A No. 14 invention to the Evidence A No. 16 invention and HIF prolyl hydroxylase of the Corrected invention 1 are different and prolyl-4-hydroxylase described in the Evidence A No. 14 invention to the Evidence A No. 16 invention shows no action against HIF, and the substance which had been known to have action for inhibiting both prolyl-4-hydroxylase described in the Evidence A No. 14 invention to the Evidence A No. 16 invention and HIF prolyl hydroxylase, is only a substance having a specific chemical structure described in Evidence A No. 6 and N-oxalylglycine described in Evidence A No. 18 (No. 5 1(5)B and C, and 10(4)A). N-oxalylglycine described in Evidence A No. 18 is different from an active ingredient of the Evidence A No. 14 invention to the Evidence A No. 16 invention, and the substance having a specific chemical structure described in Evidence A No. 6 which is included in the active ingredient of the Evidence A No. 14 invention to the Evidence A No. 16 invention, is a compound of FG-2179 in Table 1 of Evidence

A No. 6 (hereinafter referred to as "FG-2179 compound".). The FG-2179 compound corresponds to a compound, of compounds represented by formula I in the Evidence A No. 14 invention, wherein Q is O, X is O, Y is CR^3, m is 0, A is a $-CH_2-$ group, B is CO_2H, and R^1 to R^4 are hydrogen.

On this technical level, a person skilled in the art could not have easily conceived that substance described in the Evidence A No. 14 invention to the Evidence A No. 16 invention, having action for inhibiting prolyl-4-hydroxylase, other than the FG-2179 compound, has action for inhibiting HIF prolyl hydroxylase, on the original filing date of the Patent.

Further, in the Evidence A No. 14 invention, in a case where an active ingredient is a compound represented by formula I, wherein Q is O, X is O, Y is CR^3, m is 0, A is a $-CH_2-$ group, B is CO_2H, and R^1 to R^4 are hydrogen; that is to say, in a case of the FG-2179 compound, the two inventions are different in the difference feature 14-1 described in D(a) above. As it had not been known that a heterocyclic compound having a substituent of a "$-C(=O)-NH-CH_2-CO_2H$ group" in which the heterocycle is quinolone or isoquinoline has action for inhibiting HIF prolyl hydroxylase, a person skilled in the art could not have easily conceived of the difference feature on the original filing date of the Patent.

Effect for enhancing expression of erythropoietin of the Corrected invention 1 and effect for increasing blood levels are described in Examples 1, 2, 7, and 8 in the detailed description of the invention of the corrected description, effect for increasing hematocrit is described in Examples 2 to 4, and in Example 3, a compound of the Corrected invention 1 increased hemoglobin level of blood. Thus, in the corrected description, therapeutic effect on anemia with a compound of the Corrected invention 1 is specifically described, and it is recognized that the Corrected invention 1 has a prominent effect which is not obtained from respective items of Evidence A.

Therefore, it cannot be concluded that as a person skilled in the art could have easily made the Corrected invention 1 on the basis of inventions described in Evidence A No. 14 to A No. 16 and well-known art, the demandant should not be granted a patent for the invention in accordance with the provisions of Article 29(2) of the Patent Act.

F Demandant's allegation

The demandant indicates Evidence A No. 6, A No. 17 and A No. 18, and alleges

that as testing a compound inhibiting prolyl hydroxylase in collagen as a candidate for inhibiting HIF prolyl hydroxylase was performed on the original filing date of the Patent, a person skilled in the art could easily achieve to test a compound for inhibiting prolyl hydroxylase in collagen so as to obtain a compound for inhibiting HIF prolyl hydroxylase, for a purpose of treating anemia. However, there is no reasonable reason of combining main Cited Documents (Evidence A No. 14 to A No. 16), Evidence A No. 6, A No. 17, and A No. 18, and Evidence A No. 11 in which idea that degradation of HIF-1α is inhibited by inhibiting prolyl hydroxylation of HIF-1α, whereby leading to production of EPO and increasing erythrocytes is indicated. Thus, by the demandant's allegation, it cannot be concluded that a person skilled in the art could easily invent the Corrected invention 1.

G Regarding priority

The judgment described in E above is that considering evidences which were well-known between the filing date as a basis of claiming priority and the original filing date of the Patent, the Corrected invention 1 could not be easily made. Even if priority claim of the Corrected invention 1 is not approved, this does not affect the judgment. Therefore, in judgment on Reason 2 for invalidation, we do not judge the existence or absence of priority claim of the Corrected invention 1.

(2) Regarding Corrected inventions 5 to 10

The Corrected inventions 5 to 10 specify cause of anemia in the Corrected invention 1. As described in (1) above, it cannot be said that the Corrected invention 1 could be easily made based on the invention described in Evidence A No. 14, Evidence A No. 15, or Evidence A No. 16 by a person skilled in the art, and it cannot be concluded that a person skilled in the art could easily invent the Corrected inventions 5 to 10 on the basis of these inventions.

2 Reason 1 for invalidation

(1) Regarding Corrected invention 1

A Invention described in Evidence A No. 6

In Table 1 of Evidence A No. 6, a chemical formula of the FG-2179 compound is described (No. 5 1(5)A above). As in FIG. 4a of Evidence A No. 6, a band of pVHL

became light in a case of using 100 μM of the FG-2179 compound, whereby it is recognized that 100μM of the FG-2179 compound inhibits HIF PH (No. 5 1(5)B and C above). Further, in Evidence A No. 6, it is described that "A model compound of this series stabilized HIF in a variety of cells, ... " and "stabilization of HIF through the inhibition of the HIF PH, ..." (No. 5 1(2)B and (6)A above). The PH is prolyl hydroxylase from the description in No. 5 1(3) above, and HIF PH is an enzyme for hydroxylation of a proline residue in α subunit of HIF from description in No. 5 1(2)A and B above. Thus, "HIF" in "stabilization of HIF through the inhibition of the HIF PH" is "α subunit of HIF"; that is to say, "HIFα". Therefore, it is recognized that in Evidence A No. 6, the invention regarding the FG-2179 compound for inhibiting HIF prolyl hydroxylase and stabilizing HIFα is described.

B Comparison / Judgment

We will compare the Corrected invention 1 with the invention described in Evidence A No. 6.

Both inhibition of HIF prolyl hydroxylase in Corrected invention 1 and inhibition of HIF prolyl hydroxylase in the invention described in Evidence A No. 6 are to inhibit hydroxylation of proline in peptide of HIFα with HIF prolyl hydroxylase, and are common.

Comparing a heterocyclic carboxamide compound specified by formula (I) in the Corrected invention 1 with the FG-2179 compound having the chemical formula described in Table 1 of Evidence A No. 6, in formula (I) of the Corrected invention 1, X is O, A is $-CH_2-$, and B is $-CO_2H$, so that the heterocyclic carboxamide compound specified by formula (I) in the Corrected invention 1 includes a compound having a "$-C(=O)-NH-CH_2-CO_2H$ group" as a substituent. The substituent corresponds to a substituent binding to 2-position of a pyridine ring in the FG-2179 compound described in Table 1 of Evidence A No. 6.

Therefore, both correspond in inhibiting HIF prolyl hydroxylase by a heterocyclic compound having a substituent of a "$-C(=O)-NH-CH_2-CO_2H$ group". On the other hand, the two are different in that the heterocycle of the Corrected invention 1 is quinolone (a compound represented by formula (Ia)) or isoquinoline (a compound represented by formula (Ib)), whereas the heterocycle of the invention described in

Evidence A No. 6 is pyridine (difference feature 1). Further, the two are different in that in the Corrected invention 1, the FG-2179 compound is used for producing an agent for treating anemia; that is to say, the Corrected invention 1 has medicinal use for treating anemia with the FG-2179 compound, on the other hand, in the invention described in Evidence A No. 6, the FG-2179 compound has action for inhibiting enzyme activity of HIF prolyl hydroxylase and stabilizing HIFα, however, there is no description in Evidence A No. 6 that the FG-2179 compound can be used for treating anemia (difference feature 2).

We will examine the difference feature 1. The difference feature 1 is the same as the difference feature 14-1 described in (1) Reason 2 for invalidation, and it cannot be concluded that the difference feature could be easily made, as described in 1(1)E above.

Therefore, without examining whether priority claim of difference feature 2 and Corrected invention 1 is approved, it cannot be concluded that a person skilled in the art could easily invent the Corrected invention 1 on the basis of the invention described in Evidence A No. 6.

(2) Regarding Corrected inventions 5 to 10

The Corrected inventions 5 to 10 specify cause of anemia in the Corrected invention 1. As described in (1) above, it cannot be concluded that the Corrected invention 1 could be easily made based on the invention described in Evidence A No. 6 by a person skilled in the art, and it cannot be concluded that a person skilled in the art could easily invent the Corrected inventions 5 to 10 on the basis of these inventions.

3 Reason 3 for invalidation

The demandant alleges that as only examples regarding compounds of which the chemical structure are extremely similar with each other are described in the detailed description of the invention of the description of the case, a person skilled in the art must conduct a lot of experiments to confirm which compounds can be used for treating anemia, and the description of the detailed description of the invention of the description of the case does not meet the requirement stipulated in Article 36(4)(i) of the Patent Act. Further, as there is no description, in the detailed description of the invention, to support that billions of kinds of heterocyclic carboxamide compounds

described in the scope of claims can be used for treating anemia, the description of the scope of claims of the case does not meet the requirement stipulated in Article 36(6)(i) of the Patent Act.

The demandant's allegation is to allege that comparing the number of heterocyclic carboxamide compounds represented by formula (I) within the scope of claims, the number of compounds actually confirmed on treatment of anemia in Examples is low, so that the description of the detailed description of the invention of the corrected description does not meet the requirement stipulated in Article 36(4)(i) of the Patent Act, and the description of claim 1 in the scope of claims of the Patent does not meet the requirement stipulated in Article 36(6)(i) of the Patent Act. However, it cannot be concluded that the Patent does not meet the requirement stipulated in Article 36 of the Patent Act, on the ground of the number of Examples with respect to description of the scope of claims.

4 Reason 4 for invalidation

As the demandant alleges that as there is no description, in the detailed description of the invention, about examination results whether the heterocyclic carboxamide compound described in the scope of claims of the case inhibits HIF prolyl hydroxylase, the description of the detailed description of the invention of the description of the case does not meet the requirement stipulated in Article 36(4)(i) of the Patent Act, we will examine below.

(1) Regarding Corrected invention 1

As described in No. 3 above, the Corrected invention 1 is "use of a heterocyclic carboxamide compound for manufacturing an agent for treating anemia in a subject, wherein the heterocyclic carboxamide compound inhibits HIF prolyl hydroxylase, and is represented by formula (I) (Note by the body: the chemical structure is omitted) or a physiologically active salt derived therefrom", and is invention satisfying two requirements that a heterocyclic carboxamide compound represented by formula (I) is an agent for treating anemia and inhibits HIF prolyl hydroxylase. In paragraph [0017] of the detailed description of the invention of the corrected description, it is described that "The present invention is related to a method of treating, preventing, or pretreating anemia in a subject. In one embodiment, the method includes increasing endogenous

EPO; in various embodiments, this includes inhibiting enzyme activity of HIF prolyl hydroxylase." According to this description, it is understood that the two requirements of the Corrected invention 1 are that a heterocyclic carboxamide compound represented by formula (I) inhibits enzyme activity of HIF prolyl hydroxylase, and endogenous EPO is increased, thereby enabling treatment of anemia. Thus, it is recognized that "inhibiting HIF prolyl hydroxylase" in the Corrected invention 1 indicates a mechanism of pharmacological action for treating anemia with a heterocyclic carboxamide compound represented by formula (I).

In Evidence A No. 11, it is described that under conditions that cellular O_2 concentration is not hypoxic conditions, HIF-1α is subjected to prolyl hydroxylation and to degradation by proteasome finally; on the other hand, under conditions that cellular O_2 concentration is hypoxic conditions, HIF-1α dimerizes with HIF-1β and the heterodimer leads to the production of proteins that mediate physiologic responses to hypoxia. (No. 5 8(3)A above). Erythropoietin (EPO) is described as representative HIF-1 target gene in Evidence A No. 11 (No. 5 8(2)A above). It is described in, for example, Evidence A No. 7 (No. 5 5(2) above), Evidence A No. 8 (No. 5 6(2) and (3) above), Evidence A No. 9 (No. 5 7(3) above) and Evidence A No. 27 (No. 5 11(2) above) that EPO stimulates and enhances production of erythrocytes, and this description is a well-known matter. Thus, it is possible that a person skilled in the art could have conceived that one of mechanisms of action of an agent for treating anemia by inducing production of EPO and increasing erythrocytes is to inhibit degradation of HIF-1α by inhibiting prolyl hydroxylation of HIF-1α, from the description of publications distributed before the priority date of the Patent.

On the other hand, it is specifically described as Examples in the corrected description that a heterocyclic carboxamide compound of Corrected invention 1 increased endogenous EPO (Examples 1 to 3, 7 and 8), and anemia could be treated (Examples 2 to 4). Considering the technical level on the priority date of the Patent and the description of the corrected description, it had been possible on the original filing date of the Patent to reasonably presume that a mechanism of action for treating anemia by the heterocyclic carboxamide compound which inhibits enzyme activity of HIF prolyl hydroxylase. It can be confirmed in Reference Material 2 (Evidence A No. 13)

attached to the written amendment (form) dated November 11, 2010 that the heterocyclic carboxamide compound has action for inhibiting HIF prolyl hydroxylase.

Thus, regarding the detailed description of the invention of the corrected description, even if it is not described in the detailed description of the invention of the corrected description of specific data that a heterocyclic carboxamide compound of the Corrected invention 1 inhibits HIF prolyl hydroxylase, a person skilled in the art could have recognized that the heterocyclic carboxamide compound inhibits HIF prolyl hydroxylase, on the ground of the demandant's allegation, it cannot be concluded that description of the detailed description of the invention in the corrected description does not meet the requirements stipulated in Article 36(4)(i) of the Patent Act.

(2) Regarding Corrected inventions 5 to 10

The Corrected invention 1 and Corrected inventions 5 to 10 are inventions of use of a heterocyclic carboxamide compound represented by formula (I) for inhibiting HIF prolyl hydroxylase. Regarding the point, indicated by the demandant, that the examination result whether HIF prolyl hydroxylase is inhibited is not described in the detailed description of the invention, there is no difference between the Corrected invention 1 and Corrected inventions 5 to 10.

Thus, as described in (1) above, regarding the Corrected invention 1, it cannot be concluded that description of the detailed description of the invention in the corrected description does not meet the requirements stipulated in Article 36(4)(i) of the Patent Act, and it cannot be concluded that the Corrected inventions 5 to 10 do not meet the requirements stipulated in Article 36(4)(i) of the Patent Act.

5 Reason 5 for invalidation

The demandant alleges that "where an aryl radial may be substituted by 1 to 5 substituents selected from halogen, cyano, (C_2-C_{16})-alkyl, (C_1-C_{16})-alkoxy and carbamoyl" in the Corrected invention 1 is not a matter described in a Document in foreign language and not a matter which is obvious from the matter described in the Document in foreign language (allegation 1). Further, the demandant also alleges that a compound represented by formula (I) in the Corrected invention 1 is a new matter by deleting most of choices described in the Document in foreign language, and is not a matter described in Document in foreign language and not a matter which is obvious

from the matter described in the Document in foreign language (allegation 2).

(1) Regarding allegation 1

The description note by the demandant is a case where a substituent of "aryl" is specified out of choices of R^1 to R^3 in a compound represented by formula (I), and a case where a substituent of "aryl" is specified out of choices of R^3, R^{13}, R^{14}, R^{17} and R^{18} when R^1 and R^2 or R^2 and R^3, together with the pyridine carrying them, form a heterocycle represented by formula Ia or formula Ib. The former case is described, in line 50 of page 12 to line 32 of page 13 of the description in foreign language, as "where an aryl radical may be substituted by 1 to 5 substituents selected from ... halogen, cyano, ... (C_2-C_{16})-alkyl, ... (C_1-C_{16})-alkoxy, ... carbamoyl,", and is a matter described in the Document in foreign language. Regarding the latter case, it is described in line 39 to the last line of page 14 of the description in foreign language that a chemical formula when R^1 and R^2 or R^2 and R^3, together with the pyridine carrying them, form a heterocycle represented by formula Ia or formula Ib and the heterocycle is a quinoline ring, is formula Ia, and in a case that the heterocycle is isoquinoline ring, the chemical formula is formula Ib. Further, it is described in lines 1 to 2 below chemical formulas Ia and Ib on the upper column of page 15 of the description in foreign language that "the substituents R^{12} to R^{23} in each case independently of each other have the meaning of R^1, R^2 and R^3". Thus, a substituent of "aryl" of choices of R^3, R^{13}, R^{14}, R^{17} and R^{18} is the same as in the former case, and the latter case is the matter described in the Document in foreign language.

The demandant also alleges that it is not clear what "an aryl radical" indicates in the description in foreign language. However, in the description in foreign language, elements of Y are described in line 33 of page 10, and next elements of R^1 to R^3 are described. Thus, a phrase of "where an aryl radical may be substituted ..." is obviously described in the explanation of R^1 to R^3, and it is natural that "an aryl radical" above indicates all "aryl" in the description from line 34 of page 10 to the front of this phrase. Therefore, the demandant's allegation cannot be adopted.

(2) Regarding allegation 2

We will examine the element of each substituent of the compound represented by formula (I) in the Corrected invention 1.

A Regarding A

"-CH_2-" of element of A is described as "(C_1-C_4)-alkylene" (line 2 below chemical formula of page 6 in the description in foreign language), it is obvious that -CH_2- is C_1-alkylene and is included in "(C_1-C_4)-alkylene".

B Regarding B

"-CO_2H" of element of B is described in line 7 from the bottom of page 6 of the description in foreign language, and "CO_2-G carboxyl radial (where G is a radical of alcohol G-OH in which G is (C_1-C_{20})-alkyl radical or (C_7-C_{16})-carbocyclic aralkyl radical)" is described as "B is a CO_2-G carboxyl radical, where G is a radical of an alcohol G-OH in which G is selected from (C_1-C_{20})-alkyl radical, ... (C_7-C_{16})-carbocyclic aralkyl radical" (line 1 from the bottom of page 6 to line 6 of page 7 of the description in foreign language).

C Regarding X and Q

"O" of element of X is described in line 24 of page 9 of the description in foreign language, and "O" of element of Q is described in line 25 of page 9 of the description in foreign language.

D Regarding R^4

Regarding R^4, in lines 27 to 31 of page 9 of the description in foreign language, it is described that "where, if Q is O ..., R^4 is hydrogen, ... (C_7-C_{11})-aralkyl radical,", "benzyl" is "(C_7-C_{11})-aralkyl radical", it is obvious that benzyl is C_7-aralkyl radical and is included in "(C_7-C_{11})-aralkyl radical".

E Regarding Y

"CR^3" of element of Y is described in line 33 on page 10 of the description in foreign language.

F Regarding R^1, R^2 and R^3

First, elements of R^1, R^2 and R^3 of the claim 1 before Correction of the case of "hydrogen, halogen, cyano, (C_1-C_{20})-alkyl, (C_1-C_{20})-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy, carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N-((C_1-C_{18})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, or -O-$[CH_2]_xC_fH_{(2f+1-g)}F_g$" are described as "$R^1$, R^2 and R^3 are identical or different and are hydrogen, ... halogen, cyano, ... (C_1-C_{20})-alkyl, ... (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, ... (C_1-C_{20})-alkoxy, ... (C_6-C_{12})-aryloxy, ... (C_7-C_{16})-aralkyloxy, ... -O-$[CH_2]_xC_fH_{(2f+1-g)}F_g$, ... carbamoyl, N- ($C_1$-$C_{12}$)-alkylcarbamoyl, ... N-((C_1-C_{18})-alkoxy-(C_1-C_{10})-alkyl)- carbamoyl," (p. 10, line 34 to p.

11, line 32 of the description in foreign language), and f, g, x are described in lines 6 to 8 below chemical formula Id of page 15 in the description in foreign language. As described in (1) above, a substituent in which "aryl" of elements of R^1, R^2 and R^3 (including aralkyl; that is to say, arylalkyl, and aryl in aralkyloxy; that is to say, arylalkyloxy) optionally has, is described in the Document in foreign language.

Further, the point that R^1 and R^2, or R^2 and R^3, together with the pyridine carrying them, form a heterocycle represented by formula Ia or formula Ib, is described in line 39 to the last line of page 14 of the description in foreign language, as "where R^1 and R^2, or R^2 and R^3, together with the pyridine ... carrying them, form an optionally substituted heterocyclic ring systems selected from ... quinoline, isoquinoline, ...; where quinoline, isoquinoline or ... preferably satisfy the formulae Ia, Ib ...:", and chemical formulas Ia and Ib are described on page 15 (Note by the body: these chemical formulas in the description in foreign language are omitted). Below the chemical formula in the description in foreign language, it is described that "the substituents R^{12} to R^{23} in each case independently of each other have the meaning of R^1, R^2 and R^3". As described above, it is described in the description in foreign language that elements of R^1 to R^3 includes hydrogen. Formula Ia of the Corrected invention 1 is a case where R^{12} and R^{15} are hydrogen in formula Ia indicated in page 15 of the description in foreign language. Further, formula Ib of the Corrected invention 1 is a case where R^{16} and R^{19} are hydrogen in formula Ib indicated in page 15 of the description in foreign language. In addition, as elements of R^1, R^2 and R^3 of the Corrected invention 1 and elements of R^{13}, R^{14}, R^{17} and R^{18} are the same, "the substituents R^{12} to R^{23} in each case independently of each other have the meaning of R^1, R^2 and R^3" is described in the description in foreign language, and the elements of R^1, R^2 and R^3 are described in the description in foreign language, it could be concluded that elements of R^{13}, R^{14}, R^{17} and R^{18} of the Corrected invention 1 are described in the description in foreign language.

G Thus, the element of each substituent in a compound represented by formula (I) of the Corrected invention 1 is described in the Document in foreign language. The compound represented by formula (I) in the Corrected invention 1 does not introduce a new technical matter in Document in foreign language. Thus, even if heterocyclic carboxamide compounds represented by formula (I) in the Corrected invention 1 are not in complete correspondence in the description of Markush-form in Document in foreign

language by deleting some choices described in Markush-form of the Document in foreign language, it cannot be concluded that the Corrected invention 1 is not within the matters described in the Document in foreign language.

(3) Summary

As described above, it cannot be concluded that matters described in the scope of claims are not within the matters described in the Document in foreign language, on the ground of the demandant's allegation.

No. 7 Closing

As described above, all of the reasons for invalidation alleged by the demandant are groundless.

The costs in connection with the trial shall be borne by the demandant under the provisions of Article 61 of the Code of Civil Procedure which is applied mutatis mutandis in the provisions of Article 169(2) of the Patent Act.

Therefore, the trial decision shall be made as described in the conclusion.

November 18, 2015

Chief administrative judge: TAMURA, Akiteru
Administrative judge: OHTAKU, Ikuji
Administrative judge: SAITO, Megumi