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COLOMBIA

P-4437

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

Re: Expediente No. 14-169.333
Solicitud de patente a nombre de **CHUGAI SEIYAKU KABUSHIKI KAISHA**

Yo, CAROLINA DAZA MONTALVO, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 86-53, piso 6, y actuando como apoderada sustituta, de acuerdo con la sustitución adjunta, de la sociedad CHUGAI SEIYAKU KABUSHIKI KAISHA, domiciliada en Tokio, Japón, solicitante de la patente de la referencia, interpongo recurso de reposición contra la resolución No. 52620 emitida el 26 de agosto de 2015 por el Superintendente de Industria y Comercio, por medio de la cual se niega el privilegio de patente de invención para la solicitud contenida en el expediente de la referencia.

Mi mandante se permite manifestar a ese despacho que se reafirma en todos y cada uno de los argumentos que hacen parte integrante de la respuesta al oficio No. 15192 notificado por fijación en lista el 9 de diciembre de 2014, presentada ante ese despacho el 25 de febrero de 2015.

1. FUNDAMENTOS DEL RECURSO

En relación con los argumentos presentados por ese despacho en la resolución impugnada No. 52620 emitida el 26 de agosto de 2015, es necesario señalar que carecen de un enfoque adecuado de conformidad con las normas, jurisprudencia y reglas técnicas que existen para evaluar el nivel inventivo de una invención.

1.1 La indebida interpretación del artículo 18 de la Decisión 486/00

Es deseo del solicitante presentar argumentos contra las declaraciones de esa Superintendencia indicando como primera medida que el examinador no realizó una adecuada interpretación del artículo 18 de la Decisión 486/00 y parte de premisas erradas, en cuanto a la supuesta obviedad de la materia objeto de la presente invención, y realiza un equivocado análisis del requisito en cuestión, para finalmente negar sin justificación la patente para la solicitud en comento.

En este sentido, volvemos sobre el particular que el artículo 18 de la Decisión 486/00 determina que *“una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica”*. (El subrayado es nuestro).

1/16

Ae 1

Lo anterior significa que el análisis de nivel inventivo **NO** es una comparación de los objetos de las anterioridades y la solicitud en estudio. El análisis de nivel inventivo **debe demostrar** la obviedad de la invención y establecer cómo ésta no contiene un salto cualitativo, que demuestre su altura inventiva, teniendo en cuenta que se hace **necesario demostrar** que la invención analizada carece de nivel inventivo y hubiese sido obvia para una persona versada en la materia.

Considerando la definición anterior, el solicitante desea se tengan en cuenta los siguientes argumentos así como los argumentos presentados el 25 de febrero de 2015 en respuesta al oficio No. 15192 notificado por fijación en lista el 9 de diciembre de 2014, los cuales dan soporte a los dichos siguientes argumentos y demuestran que la solicitud de la referencia cumple con los requisitos de nivel inventivo.

En la resolución impugnada el examinador indica la falta de nivel inventivo de las reivindicaciones 1 a 20 a la luz de las enseñanzas descritas en los documentos D1 (TTO W., *Federation of European Biochemical Societies* 309(1), 85-88) y D2 (WO2004/039826).

El examinador indica en la resolución que el documento D1 describe un anticuerpo IgG en donde el CDR es modificado a histidina. Para el examinador, la invención de la reivindicación 1 de la presente solicitud se diferencia del anticuerpo descrito en el documento D1 en que el anticuerpo está en una composición. Sin embargo, no hay evidencia de un efecto técnico inesperado por el simple hecho de que el anticuerpo esté en una composición. Adicionalmente, según el examinador el documento D2 describe una composición que comprende un anticuerpo IgG con un CDR modificado. A la luz de estos hechos, para el examinador es obvio para una persona del oficio normalmente versada en la técnica obtener una composición del anticuerpo del documento D1. Además, las reivindicaciones 2 y 20 no contienen características adicionales que hagan inventiva la composición reclamada. De esta forma, el examinador indica que la invención reclamada por el solicitante carece de nivel inventivo a la luz del estado de la técnica citado.

Sin embargo, es deseo del solicitante indicar que el documento D2 establece claramente que los aminoácidos de los CDRs pueden ser modificados hasta un nivel en el cual su enlace al antígeno y su actividad neutralizante son retenidos (página 16, líneas 6-8). Por otro lado, el anticuerpo del documento D1 muestra una disminución de actividad de enlace cuando el antígeno está en pH ácido. Por lo tanto, no habría motivación para una persona del oficio normalmente versada en la técnica para utilizar tal anticuerpo con actividad disminuida para una composición farmacéutica. El solicitante considera que una persona del oficio normalmente versada en la técnica más bien se alejaría de utilizar tal anticuerpo para una composición farmacéutica, que también es soportado por las enseñanzas técnicas descritas en el documento D2. Así, ambos documentos D1 y D2 fallan en describir la idea técnica de la presente invención para utilizar un anticuerpo con las características reclamadas para una composición farmacéutica con el objetivo de tratamiento.

Adicionalmente, en respuesta a la posición del examinador con respecto a la ausencia de un efecto técnico inesperado, es deseo del solicitante indicar que los inventores de la

presente solicitud fueron los primeros en el mundo en descubrir que la administración a un cuerpo viviente de un anticuerpo con una actividad dependiente de pH, comparado con un anticuerpo sin tal actividad, ejerce efectos superiores tales como elongación de la vida media en la sangre y acción farmacológica extendida del anticuerpo. Esto se muestra claramente en los ejemplos incluidos por el solicitante en la descripción de la presente solicitud. Por ejemplo, el ejemplo 8 en el que se realiza *in vivo* la utilización de ratos transgénico de receptor IL-6 humano demuestra que la farmacocinética de los anticuerpos anti-IL-6 dependientes de pH (H3p1/L73, CLH5/L73, H170/L82) es mejorada en comparación con los anticuerpos no dependientes de pH (tipo salvaje: WT). Adicionalmente, el ejemplo 18 demuestra *in vivo* que la velocidad de eliminación del anticuerpo en plasma aumenta con anticuerpos anti-IL-6 dependientes de pH (H170/L82, H4v4) en comparación con anticuerpos no dependientes de pH (WT, H54/L28).

Estas características de la composición farmacéutica de la presente invención corresponden a efectos técnicos que no pudieron haber sido predichos a partir del estado de la técnica, ya que por ejemplo el documento D1 únicamente analiza la actividad *in vitro* de un anticuerpo dependiente de pH (anticuerpo que no está relacionado con el anticuerpo que se utiliza para tratamiento, es decir el anticuerpo anti-lisozima) para enlazar el antígeno.

Adicionalmente, los inventores de la presente solicitud han publicado un artículo científico en relación con la presente invención, particularmente en la revista *Nature Biotechnology* (se presenta como anexo al presente memorial), el cual ha tenido una muy buena recepción por parte de la comunidad científica. En varias opiniones se ha indicado que la presente invención es epocal para un experto en el campo técnico de los anticuerpos y es de gran valor a nivel mundial. Además, la presente solicitud antecedió solicitudes de otras compañías farmacéuticas que están dirigidas a otros anticuerpos dependientes de pH que utilizan la presente invención. Estas incluyen, por ejemplo, WO2009/139822 (anticuerpo anti-hepcidina, Amgen), WO2011/111007 (anticuerpo anti-PCSK9, Rinat Neuroscience, Pfizer), WO2014/028354 (anticuerpo anti-PCSK9, Regeneron), WO2014/144080 (anticuerpo anti-PCSK9, Amgen), WO2014/144577 (anticuerpo anti-TFPI, Bayer), WO2015/038984 (anticuerpo anti-EGFR, Halozyme), entre otras. Estas solicitudes son evidencia de la utilidad y relevancia de la presente invención en el campo de la medicina, lo cual es valorado por los expertos en la técnica. De acuerdo a esto, los inventores de la presente invención fueron los primeros en descubrir la invención cuya utilidad es científicamente e industrialmente apreciada. De esta manera, es obvio que tal invención tiene un efecto notable y es altamente inventivo.

Adicional a lo anterior, es deseo del solicitante indicar a ese Honorable Despacho que la Oficina Europea de Patentes emitió el 24 de junio de 2015 una Comunicación indicando la Intención de Concesión para la solicitud equivalente No. 09729337.7 - 1412 (copia de la Intención de Concesión se presenta como anexo al presente memorial).

De esta forma, aunque el solicitante reconoce la independencia de cada oficina de patentes, desea manifestar que le resulta sorprendente que otras oficinas de patentes hayan reconocido, todos los requisitos de patentabilidad para la invención reclamada, mientras únicamente la Superintendencia de industria y Comercio se aleja de tal opinión, siendo la novedad, el nivel inventivo y la aplicabilidad industrial conceptos totalmente universales.

En consecuencia, es claro el nivel inventivo que significó la presente invención para el estado de la técnica. Así, se reitera que la presente invención definida en las reivindicaciones 1 a 20 cumple con el requisito de nivel inventivo según los lineamientos del artículo 18 de la decisión 486/00.

Teniendo en cuenta lo dicho anteriormente, solicito a usted lo siguiente:

- a) Que de conformidad con lo previsto por los artículos 3, 42 y 80 del Código de Procedimiento Administrativo y de lo Contencioso Administrativo se consideren y se resuelvan **TODOS** los argumentos y **TODAS** las cuestiones planteadas así como las que aparezcan con motivo de este recurso,
- b) Que se revoque la resolución No. **52620** del 26 de agosto de 2015 expedida por el Superintendente de Industria y Comercio, y se proceda a conceder el privilegio de patente de invención a la solicitud de mi mandante

Señor Superintendente,


CAROLINA DAZA MONTALVO
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P-4437

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. 14-169.333

Solicitud de patente a nombre de CGUGAI SEIYAKU KABUSHIKI KAISHA

RECURSO DE REPOSICIÓN

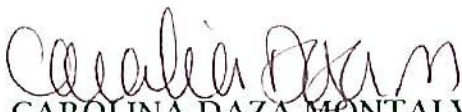
Yo, SILVANA MARÍA LÓPEZ DÍAZ, identificada como aparece al pie de mi firma, domiciliada en Bogotá, atentamente informo a usted que sustituyo el poder con que obro, a la doctora CAROLINA DAZA MONTALVO, domiciliada en Bogotá, identificada con la Cédula de Ciudadanía No.66.783.790 de Palmira Valle y portadora de la tarjeta profesional No.TP-141563 del CSJ, con las mismas facultades que me fueron conferidas para este caso.

Muy atentamente,



SILVANA MARÍA LÓPEZ DÍAZ
C.C. No. 22.468.787
TP- 147463 CSJ

Acepto sustitución



CAROLINA DAZA MONTALVO
C.C. 66.783.790 de Palmira Valle
TP-141563 CSJ

PRESENTACION PERSONAL NOTARIA **II**
El anterior escrito fué presentado ante el
NOTARIO ONCE (E) DEL CÍRCULO DE BOGOTÁ D.C.

Personalmente por: Silvana Manc
Wiper Diaz
quien exhibió la C.C. 22468787 Baculo
y Tarjeta Profesional No. 147463 C.S.J.

Fecha: [Signature]
Firma: [Signature]

Mauricio Mora Tejada
NOTARIO (E)

26 JUN 2015



ANEXOS

- Igawa y otros (2010) *Nature Biotechnology* 28(11), 1203-1207.
- Comunicación informando Intención de Concesión de solicitud equivalente en Europa No. 09729337.7 - 1412

Antibody recycling by engineered pH-dependent antigen binding improves the duration of antigen neutralization

Tomoyuki Igawa, Shinya Ishii, Tatsuhiko Tachibana, Atsuhiko Maeda, Yoshinobu Higuchi, Shin Shimaoka, Chifumi Moriyama, Tomoyuki Watanabe, Ryoko Takubo, Yoshiaki Doi, Tetsuya Wakabayashi, Akira Hayasaka, Shoujiro Kadono, Takuya Miyazaki, Kenta Haraya, Yasuo Sekimori, Tetsuo Kojima, Yoshiaki Nabuchi, Yoshinori Aso, Yoshiki Kawabe & Kunihiro Hattori

For many antibodies, each antigen-binding site binds to only one antigen molecule during the antibody's lifetime in plasma. To increase the number of cycles of antigen binding and lysosomal degradation, we engineered tocilizumab (Actemra)¹, an antibody against the IL-6 receptor (IL-6R), to rapidly dissociate from IL-6R within the acidic environment of the endosome (pH 6.0) while maintaining its binding affinity to IL-6R in plasma (pH 7.4). Studies using normal mice and mice expressing human IL-6R² suggested that this pH-dependent IL-6R dissociation within the acidic environment of the endosome resulted in lysosomal degradation of the previously bound IL-6R while releasing the free antibody back to the plasma to bind another IL-6R molecule. In cynomolgus monkeys, an antibody with pH-dependent antigen binding, but not an affinity-matured variant, significantly improved the pharmacokinetics and duration of C-reactive protein inhibition. Engineering pH dependency into the interactions of therapeutic antibodies with their targets may enable them to be delivered less frequently or at lower doses.

Therapeutic antibodies now offer important treatment options for many diseases^{3,4}. Although most antibodies effectively neutralize their cognate antigens, relatively high doses and/or frequent injections are required to achieve therapeutic efficacy when targeting antigens, such as IL-6R⁵, EGFR⁶, IgE⁷, CD4 (ref. 8) and CD40 (ref. 9), with high rates of synthesis. Antibodies targeting these antigens show significant antigen-mediated clearance. For many conventional antibodies, each antigen-binding site binds to only one antigen molecule during the antibody's lifetime in plasma. Because their cognate antigens are usually produced continuously *in vivo*, the minimum number of antigen-binding sites required to completely neutralize the function of the antigen cannot be less than the amount of antigen that is produced between doses. This restricts the dose and dosing frequency of many therapeutic antibodies. For most antibodies, improving the binding affinity¹⁰ and the pharmacokinetics by increasing binding to the neonatal Fc receptor (FcRn)^{11–13} is, to some extent, effective for reducing the therapeutic dose and/or the dosing frequency. Nonetheless, the extent of such

improvements hits a ceiling defined by the limited number of antigen-binding events per antibody molecule and the rate at which the antigen continues to be produced. Further improvement can only be achieved by increasing the number of cycles in which an antibody binds to and releases the antigen for subsequent lysosomal degradation and thereby increasing the amount of antigen that can be bound by a single antigen-binding site. To date, although various technologies for optimizing antibody therapeutics have been reported¹⁴, there is no technology for increasing the number of cycles of antigen binding and lysosomal degradation.

Tocilizumab, a humanized IgG antibody against IL-6R that is approved for treating moderate to severe rheumatoid arthritis¹, exhibits a high rate of antigen-mediated clearance *in vivo* as a result of the high turnover of IL-6R following its delivery⁵. There are both membrane-bound (mIL-6R) and soluble (sIL-6R) forms of IL-6R. Both transduce IL-6 signaling by means of gp130 (ref. 15) and both are targeted by tocilizumab. We engineered unmodified tocilizumab¹⁶ (TCZ) to dissociate from IL-6R within the acidic environment of the endosome by decreasing its binding affinity at pH 5.5–6.0 (ref. 17), without affecting its binding affinity to IL-6R in plasma at pH 7.4. Previous studies have shown that engineering cytokine ligands to dissociate from their receptors rescued the ligands from lysosomal degradation *in vitro*^{18,19}. Therefore, we expected that enabling dissociation of the antibody from IL-6R within the endosome would rescue the antibody from lysosomal degradation, enabling free antibody to be recycled back to the cell surface (for release to the plasma *in vivo*) in order to bind to another IL-6R molecule.

We subjected all residues in the complementarity determining regions and several framework residues important for antigen binding to histidine scanning to identify histidine mutations that confer pH-dependent binding of IL-6R. Histidine, which has a pK_a of approximately pH 6, is often found at the interfaces between proteins that interact with different affinities in plasma and endosomes²⁰. Surface plasmon resonance (SPR) identified several histidine mutations that conferred pH-dependent binding of TCZ to IL-6R. Separate mutation of Tyr27, Ser31 and Trp35 to His in the heavy chain variable region and separate mutation of Asp28, Tyr32, Arg53 to His and His55 to Leu in the light chain variable

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Received 31 August; accepted 23 September; published online 17 October 2010; doi:10.1038/nbt.1691

LETTERS

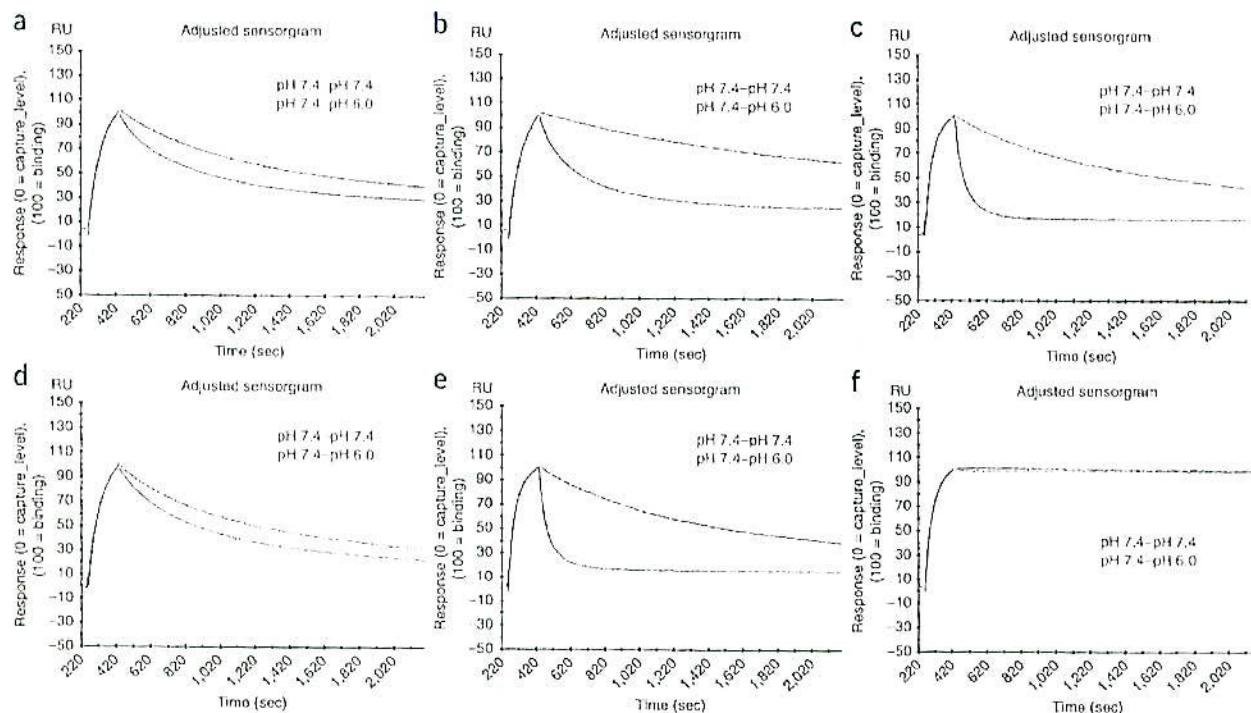


Figure 1 Surface plasmon resonance (SPR) sensorgrams of tocilizumab (TCZ), two variants with pH-dependent binding to hIL-6R (PH1, PH2), TCZ and PH2 with increased affinity to FcRn (TCZ-FcRn, PH2-FcRn) and an affinity matured variant with increased affinity to FcRn (AM-FcRn). (a–f) SPR measurements of hIL-6R association (3 min) at pH 7.4 and dissociation (30 min) at pH 7.4 (pH 7.4–pH 7.4; green), and hIL-6R association at pH 7.4 (3 min) and dissociation at pH 6.0 (30 min) (pH 7.4–pH 6.0; red) are shown for TCZ (a), PH1 (b), PH2 (c), TCZ-FcRn (d), PH2-FcRn (e) and AM-FcRn (f).

region influenced the pH dependency of IL-6R binding (positions numbered in Kabat numbering). A combination of various mutations including mutations at Tyr27, Ser31 and Trp35 in the heavy chain and Asp28, Tyr32 and Arg53 in the light chain generated the TCZ variant PH1, and mutations at Tyr27 and Ser31 in the heavy chain and Tyr32, Arg53 and His55 in the light chain generated PH2. SPR measurements of all TCZ variants used in this study are shown in Figure 1. The results indicated that the respective binding affinities of PH1 and PH2 to human soluble IL-6R (hsIL-6R) at pH 7.4 were 2.3- and 2.8-times stronger than that of TCZ. In contrast, their respective binding affinities at pH 6.0 were substantially less than that of TCZ (3.8- and 3.7-times lower). Ratios of binding affinities determined at pH 6.0 and pH 7.4 (K_D s) were ~19 and ~22 for PH1 and PH2, respectively, compared to ~2 for TCZ (Table 1). After binding to hIL-6R at pH 7.4, subsequent rapid dissociation from hIL-6R at pH 6.0 was observed for PH1 and PH2, but not for TCZ (Fig. 1a–c).

As TCZ, PH1 and PH2 do not bind to mouse IL-6R, they were administered intravenously to transgenic mice expressing human IL-6R (hIL-6R)². We measured serum amyloid A (SAA) as a pharmacodynamic marker of IL-6R neutralization²¹ after intraperitoneal injection of human IL-6 (hIL-6). This model exhibits an hIL-6-dependent increase in SAA, which was inhibited by TCZ at plasma TCZ concentrations >10 µg/ml (Supplementary Fig. 1a–b). We obtained time profiles for changes in the plasma concentrations of antibody (Fig. 2a) and SAA (Fig. 2b), as well as the associated pharmacokinetic parameters (Supplementary Table 1). The PH1 and PH2 variants of TCZ, which exhibit pH-dependent binding to IL-6R, exhibited a significant improvement in pharmacokinetics and duration of SAA inhibition compared to TCZ. The slight improvement for PH2 compared to PH1 may be due to more rapid dissociation from IL-6R at pH 6.0 (larger k_d at pH 6.0) or to greater pH dependency of binding affinity (larger K_D ratio of pH 6.0/pH 7.4) (Table 1). In this study group, the increase in SAA levels could not be inhibited by TCZ at 54 h because

Table 1 Binding kinetics of TCZ, pH-dependent binding variants and affinity matured variant to hIL-6R

Antibody	pH 7.4			pH 6.0			k_d (pH 6.0) ratio vs. TCZ	K_D ratio pH 6.0/pH 7.4
	k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (M)	k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (M)		
TCZ	$2.2E+05$	$1.1E-03$	$5.1E-09$	$2.1E+05$	$2.3E-03$	$1.1E-08$	–	2.1
PH1	$2.6E+05$	$5.7E-04$	$2.2E-09$	$1.0E+05$	$4.3E-03$	$4.2E-08$	1.9	18.9
PH2	$5.3E+05$	$1.0E-03$	$1.9E-09$	$3.5E+05$	$1.5E-02$	$4.1E-08$	6.3	22.1
TCZ-FcRn	$2.8E+05$	$1.3E-03$	$4.7E-09$	$2.1E+05$	$2.6E-03$	$1.2E-08$	1.1	2.6
PH2-FcRn	$5.6E+05$	$1.0E-03$	$1.8E-09$	$3.8E+05$	$1.5E-02$	$4.0E-08$	6.6	22.1
AM-FcRn	$5.7E+05$	$2.9E-05$	$5.2E-11$	$7.8E+05$	$1.4E-05$	$1.8E-11$	0.006	0.4

Association rate (k_a), dissociation rate (k_d) and binding affinity (K_D) of TCZ, PH1, PH2, TCZ-FcRn, PH2-FcRn and AM-FcRn to hIL-6R at pH 7.4 and pH 6.0, their TCZ to variant k_d at pH 6.0 ratio, and their pH 6.0 to pH 7.4 binding affinity (K_D) ratio are shown.

the plasma TCZ concentration at 54 h was $<10 \mu\text{g/ml}$. A slightly higher SAA concentration in the TCZ group compared to the control (IL-6 + vehicle) group at 78 h most likely resulted from a lower SAA concentration for the control group in this specific study group (normally the concentration of SAA for the control group is $\sim 200 \mu\text{g/ml}$).

As IL-6R exists in membrane-bound and soluble forms¹⁵, we used normal mice for separate evaluation of the effects of pH-dependent dissociation from mIL-6R and sIL-6R. The effect of pH-dependent binding on mIL-6R was evaluated by comparing the pharmacokinetics of TCZ and PH2 in hIL-6R transgenic mice and normal mice. In normal mice, both TCZ and PH2 exhibited longer plasma persistence than in hIL-6R transgenic mice because of the absence of human mIL-6R-mediated clearance (Fig. 2c and Supplementary Table 2). Although the profile of changes in the plasma concentration of PH2 was significantly better than that of TCZ in hIL-6R transgenic mice (20-fold higher plasma concentration at 78 h), the levels were comparable in normal mice (1.2-fold higher plasma concentration on day 14). This demonstrates that the improvement had been mainly due to the reduced clearance mediated by human mIL-6R. In other words, TCZ binds to mIL-6R and is removed from plasma by internalization and subsequent lysosomal degradation (that is, mIL-6R-mediated clearance). Degradation of antibody as a complex with mIL-6R allows a single antigen binding site to bind to only one mIL-6R molecule during its lifetime in plasma (Supplementary Fig. 2a). On the other hand, the improved pharmacokinetics exhibited by PH2 in hIL-6R transgenic mice suggests that mIL-6R-mediated clearance is reduced because the antibody is recycled back to plasma after being internalized by the mIL-6R. After it dissociates from mIL-6R in the acidic endosome, the antibody is recycled back to the plasma and can bind to another mIL-6R molecule. In contrast, the mIL-6R in the endosome is targeted for lysosomal degradation, thereby allowing a single antibody to repeatedly neutralize multiple mIL-6R molecules (Supplementary Fig. 2b).

The effect of pH-dependent binding on sIL-6R was evaluated by administration of hsIL-6R to normal mice either on its own or together with TCZ or PH2. Considering the binding affinity and amount of TCZ and PH2, we predicted that 99.6% and 99.9% of hsIL-6R should be bound to the antibody in the administration solution. A time profile of changes in hsIL-6R plasma concentration and the associated pharmacokinetic parameters are shown in Figure 2d and Supplementary Table 3, respectively. The binding of soluble antigen to antibody is reported to reduce the clearance of antigen as the antibody, with a long half-life, serves as a carrier for the antigen²². As expected, although hsIL-6R alone showed rapid clearance, clearance of hsIL-6R was reduced by 39-fold when hsIL-6R was administered together with TCZ. In contrast, although clearance for TCZ and PH2 were comparable (Supplementary Table 2), the clearance of hsIL-6R in complex with PH2 was enhanced sixfold compared to hsIL-6R in complex with TCZ, resulting in a 40-fold lower concentration of hsIL-6R in plasma on day 4. As the binding affinity of PH2 is 2.8-fold stronger than that of TCZ at pH 7.4, increased clearance of

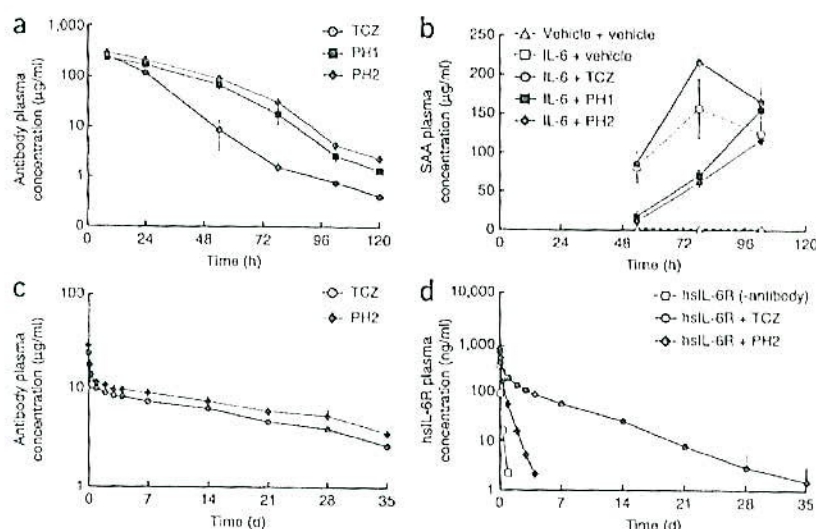


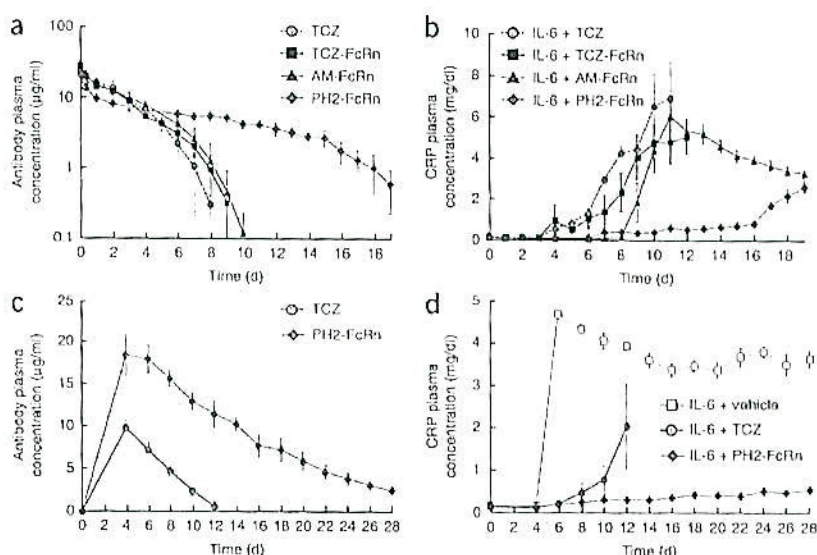
Figure 2 *In vivo* characterization of pH-dependent binding variants in mice. (a,b) *In vivo* study of TCZ, PH1 and PH2 in hIL-6R transgenic mice. TCZ, PH1 and PH2 were administered intravenously at single doses of 25 mg/kg. 4 μg/kg of hIL-6 was intraperitoneally administered at 48 h, 72 h and 96 h for TCZ, PH1, PH2 and hIL-6 control (IL-6 + vehicle) group. Vehicle group was injected with buffer, instead of antibody and hIL-6 (vehicle + vehicle). The concentration of SAA was measured as a marker of neutralization of hIL-6R²¹. Time profiles of plasma antibody concentration (a) and plasma SAA concentration (b) are shown. Each data point represents the mean $\pm$ s.d. for antibody concentration and mean $\pm$ s.e.m. for SAA concentration ($n = 3-4$ each). (c,d) *In vivo* study of TCZ and PH2 in normal mice. hsIL-6R, TCZ + hsIL-6R and PH2 + hsIL-6R were intravenously administered at single doses of 50 μg/kg for hsIL-6R and 1 mg/kg for antibody. Time profiles of plasma antibody concentration (c) and plasma hsIL-6R concentration (d) are shown. Each data point represents the mean $\pm$ s.d. ($n = 3$ each).

hsIL-6R in complex with PH2 is not derived from the presence of more free hsIL-6R, but from the pH-dependent dissociation of hsIL-6R in acidic endosomes. In other words, a complex comprising TCZ and sIL-6R would be taken up by endothelial cells in a nonspecific manner, bind to FcRn and be recycled back to plasma as a complex. This would reduce the clearance of sIL-6R and allow a single antigen binding site to bind to only one sIL-6R molecule during its lifetime in plasma (Supplementary Fig. 2c). On the other hand, our study suggests that PH2 dissociates from sIL-6R within the endosome and sIL-6R is then degraded by the lysosome. The antibody, however, is recycled back to plasma by FcRn, and recycled free antibody in plasma can bind to another sIL-6R molecule, thereby enhancing the clearance of sIL-6R and allowing a single antibody to repeatedly neutralize multiple sIL-6R molecules (Supplementary Fig. 2d). These studies on mIL-6R and sIL-6R suggest that engineering a pH-dependent binding of TCZ prolonged the pharmacokinetics and SAA inhibition in hIL-6R transgenic mice by allowing the antibody to dissociate from mIL-6R and sIL-6R in acidic endosomes. In both cases, dissociated free antibody would be recycled back to plasma and reused for binding to another IL-6R, thereby enhancing the turnover of IL-6R binding and prolonging the duration of IL-6R neutralization.

We next compared the *in vivo* effect of engineering a pH-dependent binding with the more common approach of improving antigen binding affinity in a cynomolgus monkey model. We affinity matured TCZ by introducing multiple mutations in the variable region using standard procedure¹⁰. To reduce nonantigen-mediated clearance, TCZ, an affinity-matured variant (AM), and PH2 were further engineered to improve their binding to human FcRn at pH 6.0 (ref. 12). This generated constructs TCZ-FcRn, AM-FcRn and PH2-FcRn, respectively. Owing to the N434A mutation introduced in these Fc-engineered variants, these variants exhibited an approximately three- to fourfold

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Figure 3 *In vivo* characterization of pH dependent binding variants in cynomolgus monkeys. (a,b) *In vivo* study of TCZ, TCZ-FcRn, PH2-FcRn and AM-FcRn in cynomolgus monkeys. TCZ, TCZ-FcRn, PH2-FcRn and AM-FcRn were intravenously administered at single doses of 1 mg/kg. TCZ-FcRn, PH2-FcRn and AM-FcRn were engineered to improve binding to FcRn. 5 µg/kg of cynomolgus IL-6 was subcutaneously administered daily from day 3 to day 10 for TCZ, from day 3 to day 11 for PH2-FcRn and AM-FcRn. The concentration of CRP was measured as a marker of neutralization of IL-6R. Time profiles of plasma antibody concentration (a) and plasma CRP concentration (b) are shown. Each data point represents the mean $\pm$ s.d. for antibody concentration and mean $\pm$ s.e.m. for CRP concentration ($n = 3-4$ each). (c,d) *In vivo* study of TCZ and PH2-FcRn in cynomolgus monkeys. TCZ, PH2-FcRn and vehicle were subcutaneously administered at single doses of 2 mg/kg. 5 µg/kg of cynomolgus IL-6 was subcutaneously administered every other day from day 5 to day 27. CRP concentration was measured as a marker of neutralization of IL-6R. Time profiles of plasma antibody concentration (c) and plasma CRP concentration (d) are shown. Each data point represents the mean $\pm$ s.d. for antibody concentration and mean $\pm$ s.e.m. for CRP concentration ($n = 2-5$ each). Time points when cynomolgus monkey anti-TCZ antibodies or anti-PH2-FcRn antibodies were detected in the plasma were not used for calculating mean concentration.



stronger binding affinity to human FcRn than their counterparts (data not shown). The affinity and pH dependency of the PH2-FcRn to hIL-6R binding were similar to these features of the parental PH2 molecule. The affinity of the AM-FcRn to hIL-6R binding was ~100-fold stronger than that of either TCZ or TCZ-FcRn, and AM-FcRn exhibited little pH dependency (Table 1 and Fig. 1d-f). The binding affinities and pH dependencies of binding of these antibodies to cynomolgus monkey sIL-6R was similar to that of hIL-6R (data not shown). TCZ, TCZ-FcRn, PH2-FcRn and AM-FcRn were intravenously administered to cynomolgus monkeys, each at a dose of 1 mg/kg. Cynomolgus IL-6 was injected, and the abundance of C-reactive protein (CRP) was measured as a pharmacodynamic marker of IL-6R neutralization²³. Time profiles for changes in antibody and CRP plasma concentrations are shown in Figure 3a and Figure 3b, respectively, and the associated pharmacokinetic parameters are shown in Supplementary Table 4. Comparison between TCZ and TCZ-FcRn demonstrated that increasing FcRn binding affinity to reduce non-antigen-mediated clearance improved the pharmacokinetics and duration of IL-6R neutralization by only a small extent. This is most likely because antigen-mediated clearance was the major contribution to the clearance at 1 mg/kg. Notably, compared with TCZ-FcRn, AM-FcRn (which has ~100-fold improved affinity for IL-6R) did not improve the pharmacokinetics, and only a small improvement in the duration of IL-6R neutralization could be achieved. The significant improvement in both pharmacokinetics and duration of IL-6R neutralization could be achieved by the enhanced antigen binding turnover derived from pH-dependent binding in PH2-FcRn. As AM-FcRn has a very high affinity (52 pM) and increasing the binding affinity to FcRn has improved the nonantigen-mediated clearance, the duration of IL-6R neutralization by 1 mg/kg of AM-FcRn (8 d) would be near the maximum for a conventional antibody. Presumably, the amount of IL-6R turned over in 8 d is close to the amount of antigen binding sites of 1 mg/kg of antibody. On the other hand, PH2-FcRn exhibited sustained IL-6R neutralization for 16 d, a level that could not be achieved by a conventional antibody without antigen binding turnover.

IL-6R blockade by TCZ is reported to be efficacious in treating rheumatoid arthritis¹. As subcutaneous injection at a reduced dosing frequency is especially desirable for such chronic diseases, we injected cynomolgus monkeys subcutaneously with TCZ and PH2-FcRn, each at a dose of 2 mg/kg. Time profiles for changes in the antibody and CRP plasma concentrations are shown in Figure 3c and Figure 3d, respectively, and the associated pharmacokinetic parameters are shown in Supplementary Table 5. Whereas 2 mg/kg of TCZ inhibited CRP for ~1 week, 2 mg/kg of PH2-FcRn inhibited CRP for at least 4 weeks. As CRP is an efficient marker for IL-6R blockade by tocilizumab²⁴, this result suggests that PH2-FcRn could provide clinical benefits when administered subcutaneously once a month. Superior pharmacokinetics and improved duration of IL-6R neutralization of PH2-FcRn compared to TCZ were also observed in hIL-6R transgenic mice (Supplementary Fig. 3a-b).

To quantitatively understand the improved pharmacokinetics of PH2-FcRn relative to TCZ in cynomolgus monkey, we fitted the plasma concentration time profiles of TCZ and PH2-FcRn at various i.v. doses to an antigen-mediated clearance and recycling model (Supplementary Fig. 4). The parameters obtained for TCZ and PH2-FcRn are shown in Supplementary Table 6. We determined the relative recycling ratio of the antibody from the endosome to be 0.75 for PH2-FcRn. This indicates that 75% of the internalized antibody is recycled back to plasma as a free antibody compared to TCZ. The nonantigen-mediated elimination rate of antibody was 1.2-fold lower for PH2-FcRn than for TCZ. This difference is largely due to increased binding to FcRn. We propose that a combination of pH-dependent IL-6R binding to reduce the antigen-mediated clearance and increased binding affinity to FcRn to reduce the non-antigen-mediated clearance contributed cooperatively to improve the antibody pharmacokinetics.

Although it remains to be seen how broadly the strategy used in our study can be extended, we believe that engineering pH-dependent antigen binding should improve the duration of antigen neutralization of other therapeutic antibodies. A combination of pH-dependent

binding with affinity maturation and Fc-engineering to increase binding to FcRn should further enhance the clinical potential of many antibody drugs. In this study, pH-dependent binding antibody was generated by histidine scanning. As the dissociation of an antibody from the antigen within the endosome requires destabilization of antibody-antigen interaction upon protonation of the histidine residues in the acidic pH, the feasibility of engineering pH-dependent antigen binding antibody by incorporating histidine residues may depend on electrostatic features of the antigen epitope. Nevertheless, we have successfully applied the same histidine scanning approach to two other antibodies that target different antigens (data not shown). In one of these cases, we achieved pH-dependent binding with picomolar affinity at pH 7.4 (data not shown). These findings suggest the broader potential of the approach to target antigens with high rates of *in vivo* turnover. Until now, these targets have been relatively recalcitrant to efforts based on simply increasing the affinities of therapeutic antibodies for their targets. This approach also seems well-suited to reducing the frequency and/or the size of doses required for currently approved antibody therapeutics.

METHODS

Methods and any associated references are available in the online version of the paper at <http://www.nature.com/naturebiotechnology/>.

Accession codes. GenBank: AB591055-AB591062.

Note: Supplementary information is available on the Nature Biotechnology website.

ACKNOWLEDGMENTS

We thank T. Kishimoto at the Graduate School of Frontier Biosciences, Osaka University and T. Taga at the Kumamoto University Graduate School of Medical Sciences for kindly providing human IL-6R transgenic mice; colleagues in Chugai Research Institute for Medical Science, Inc., O. Ueda, T. Tachibe, M. Kakefuda and K. Jishage for breeding human IL-6R transgenic mice, T. Matsura, M. Hiranuma, T. Koike, R. Takemoto, H. Azabu, T. Sakamoto, H. Sano and M. Kawahara for carrying out *in vivo* experiments, and M. Fujii and A. Maeno for antibody vector construction, expression and purification; and colleagues in Chugai Pharmaceutical Co. Ltd., K. Kasutani, F. Mimoto and K. Esaki for carrying out *in vitro* experiments.

AUTHOR CONTRIBUTIONS

T.I. led the overall pH-dependent binding antibody program, designed experiments, generated tocilizumab variants and wrote the manuscript. S.I. and A.M. generated tocilizumab variants. T.T., R.T., Y.H. and K. Haraya performed *in vivo* studies. S.S. led the anti-IL-6R antibody program. C.M. and A.H. performed affinity analysis of tocilizumab variants. T. Watanabe performed *in vitro* studies of tocilizumab variants. Y.D. and T. Wakabayashi performed purification of tocilizumab variants. S.K. and T.M. provided structural information for designing tocilizumab variants. Y.S., T.K., Y.N., Y.A., Y.K., and K. Hattori provided direction and guidance for the various functional areas.

COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details accompany the full-text HTML version of the paper at <http://www.nature.com/naturebiotechnology/>.

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- Mircic, M. & Kavanaugh, A. The clinical efficacy of tocilizumab in rheumatoid arthritis. *Drugs Today (Barc)* **45**, 189–197 (2009).
- Hirota, H., Yoshida, K., Kishimoto, T. & Taga, T. Continuous activation of gp130, a signal-transducing receptor component for interleukin 6-related cytokines, causes myocardial hypertrophy in mice. *Proc. Natl. Acad. Sci. USA* **92**, 4862–4866 (1995).
- Chan, A.C. & Carter, P.J. Therapeutic antibodies for autoimmunity and inflammation. *Nat. Rev. Immunol.* **10**, 301–316 (2010).
- Weiner, L.M., Surana, R. & Wang, S. Monoclonal antibodies: versatile platforms for cancer immunotherapy. *Nat. Rev. Immunol.* **10**, 317–327 (2010).
- Ohsugi, Y. & Kishimoto, T. The recombinant humanized anti-IL-6 receptor antibody tocilizumab, an innovative drug for the treatment of rheumatoid arthritis. *Expert Opin. Biol. Ther.* **8**, 659–681 (2008).
- Tabrizi, M.A., Tserg, C.M. & Roskos, L.K. Elimination mechanisms of therapeutic monoclonal antibodies. *Drug Discov. Today* **11**, 81–88 (2006).
- Tabrizi, M., Bornstein, G.G. & Suria, H. Biodistribution mechanisms of therapeutic monoclonal antibodies in health and disease. *AAPS J.* **12**, 33–43 (2010).
- Ng, C.M., Stefanich, E., Anand, B.S., Fielder, P.J. & Vaickus, L. Pharmacokinetics/pharmacodynamics of nondepleting anti-CD4 monoclonal antibody (TRX1) in healthy human volunteers. *Pharm. Res.* **23**, 95–103 (2006).
- Kelley, S.K. *et al.* Preclinical pharmacokinetics, pharmacodynamics, and activity of a humanized anti-CD40 antibody (SGN-40) in rodents and non-human primates. *Br. J. Pharmacol.* **148**, 1116–1123 (2006).
- Bostrom, J., Lee, C.V., Haber, L. & Fuh, G. Improving antibody binding affinity and specificity for therapeutic development. *Methods Mol. Biol.* **525**, 353–376 (2009).
- Dall'Acqua, W.F., Klener, P.A. & Wu, H. Properties of human IgG1s engineered for enhanced binding to the neonatal Fc receptor (FcRn). *J. Biol. Chem.* **281**, 23514–23524 (2006).
- Deng, R. *et al.* Pharmacokinetics of humanized monoclonal anti-tumor necrosis factor- α antibody and its neonatal Fc receptor variants in mice and cynomolgus monkeys. *Drug Metab. Dispos.* **38**, 600–605 (2010).
- Zalavsky, J. *et al.* Enhanced antibody half-life improves *in vivo* activity. *Nat. Biotechnol.* **28**, 157–159 (2010).
- Beck, A., Wurch, T., Bailly, C. & Corvaia, N. Strategies and challenges for the next generation of therapeutic antibodies. *Nat. Rev. Immunol.* **10**, 345–352 (2010).
- Rose-John, S., Scheller, J., Elson, G. & Jones, S.A. Interleukin-6 biology is coordinated by membrane-bound and soluble receptors: role in inflammation and cancer. *J. Leukoc. Biol.* **80**, 227–236 (2006).
- Sato, K. *et al.* Reshaping a human antibody to inhibit the interleukin 6-dependent tumor cell growth. *Cancer Res.* **15**, 851–856 (1993).
- Maxfield, F.R. & McGraw, T.E. Endocytic recycling. *Nat. Rev. Mol. Cell Biol.* **5**, 121–132 (2004).
- Sarkar, C.A. *et al.* Rational cytokine design for increased lifetime and enhanced potency using pH-activated "histidine switching". *Nat. Biotechnol.* **20**, 908–913 (2002).
- Maeda, K., Kato, Y. & Sugiyama, Y. pH-dependent receptor/ligand dissociation as a determining factor for intracellular sorting of ligands for epidermal growth factor receptors in rat hepatocytes. *J. Control. Release* **82**, 71–82 (2002).
- Burmeister, W.P., Huber, A.H. & Bjorkman, P.J. Crystal structure of the complex of rat neonatal Fc receptor with Fc. *Nature* **372**, 379–383 (1994).
- Mihara, M. *et al.* Anti-interleukin 6 receptor antibody inhibits murine AA-amyloidosis. *J. Rheumatol.* **31**, 1132–1138 (2004).
- Finkelman, F.D. *et al.* Anti-cytokine antibodies as carrier proteins. Prolongation of *in vivo* effects of exogenous cytokines by injection of cytokine-anti-cytokine antibody complexes. *J. Immunol.* **151**, 1235–1244 (1993).
- Shinkura, H. *et al.* *In vivo* blocking effects of a humanized antibody to human interleukin-6 receptor on interleukin-6 function in primates. *Anticancer Res.* **18**, 1217–1221 (1998).
- Genovese, M.C. *et al.* Interleukin 6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum.* **58**, 2968–2980 (2008).



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Application No. 09 729 337.7 - 1412	Ref. S2911 EP S3	Date 24.06.2015
Applicant Chugai Seiyaku Kabushiki Kaisha		

Communication under Rule 71(3) EPC

1. Intention to grant

You are informed that the Examining Division intends to grant a European patent on the basis of the above application with the text and drawings and the related bibliographic data as indicated below.

A copy of the relevant documents is enclosed.

1.1 Auxiliary Request 1

In the text for the Contracting States:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO
SE SI SK TR

Description, Pages

5-10, 21, 33, 35, 40, filed with entry into the regional phase before the EPO
54, 60, 62, 67-108

1-3, 3a, 4, 11-20, 22-32, 34, 36-39, 41-53, 55-59, 61, 63-66	received on	17-12-2013 with letter of	16-12-2013
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Sequence listings, SEQ ID NO

1-70 as published

Claims, Numbers

1, 2	received on	05-05-2015 with letter of	04-05-2015
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Drawings, Sheets

1/29-29/29

filed with entry into the regional phase before the EPO

Comments

The prior art has been introduced on p.3. The description has been adapted to AR1 (p.3a - part (c) deleted).

See also comments on the enclosed EPO Form 2906.

1.2 Bibliographic data

The title of the invention in the three official languages of the European Patent Office, the international patent classification, the designated Contracting States, the registered name(s) of the applicant(s) and the other bibliographic data are shown on the **enclosed EPO Form 2056**.

1.3 Observations by third parties

The third-party observations received on **23-01-2014, 14-10-2014, 22-02-2015, 09-03-2015, 13-05-2015, 28-05-2015** were found to be relevant, but in the light of the subsequent submissions from the applicant are no longer considered to be relevant.

2. Invitation

You are invited, **within a non-extendable period of four months** of notification of this communication,

2.1 to EITHER approve the text communicated above and verify the bibliographic data (R. 71(5) EPC)

(1) by filing a translation of the claim(s) in the other two official languages of the EPO

	Fee code	EUR
(2a) by paying the fee for grant including the fee for publication: minus any amount already paid (R. 71a(5) EPC):	007	915.00 0.00
Total amount:		915.00
(3) by paying additional claims fees under Rule 71(4) EPC; number of claims fees payable: 0 minus any amount already paid (R. 71a(5) EPC):	016	0.00 0.00
Total amount:		0.00

Important: If the translations of the claims and fees have already been filed and paid respectively in reply to a previous communication under Rule 71(3) EPC, e.g. in the case of resumption of examination after approval (see Guidelines C-V, 6), **agreement as to the text to be granted** (R. 71a(1) EPC) must be expressed within the same time limit (e.g. by approving the text and verifying the bibliographic data, by confirming that grant proceedings can go ahead with the documents on file and/or by stating which translations of the claims already on file are to be used).

Note 1: See "Important notes concerning fee payments" below.

Note 2: Any overpaid "minus" amounts will be refunded when the decision to grant (EPO Form 2006A) has been issued.

2.2 OR, in the case of disapproval, to request reasoned amendments or corrections to the text communicated above or keep to the latest text submitted by you (R. 71(6) EPC).

In this case the translations of the claims and fee payments mentioned under point 2.1 above are NOT due.

The terms "amendment(s)" and "correction(s)" refer only to amendments or corrections of the application documents and not of other documents (e.g. bibliographic data, the designation of the inventor, etc.).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

2.3 Bibliographic data

Where you request a change or correction of bibliographic data in response to the Rule 71(3) communication, this will **not** cause the sending of a second communication under Rule 71(3) EPC. You will still have to pay the fees and file translations in reply to the Rule 71(3) communication in the case of 2.1 above, unless you also file a reasoned request for amendments or corrections in response to the Rule 71(3) communication (see case 2.2 above).

3. Loss of rights

If neither of the two possible actions above (see points 2.1 or 2.2) is performed in due time, the European patent application will be deemed to be withdrawn (R. 71(7) EPC).

4. Further procedure

4.1 In the case of point 2.1 above

4.1.1 The decision to grant the European patent will be issued, and the **mention of the grant of the patent will be published in the European Patent Bulletin, if the requirements concerning the translation of the claims and the payment of all fees are fulfilled and there is agreement as to the text to be granted (R. 71a(1) EPC).**

Note on payment of the renewal fee:

If a renewal fee becomes due before the next possible date for publication of the mention of the grant of the European patent, publication will be effected only after the renewal fee and any additional fee have been paid (R. 71a(4) EPC).

Under Article 86(2) EPC, the obligation to pay renewal fees to the European Patent Office terminates with the payment of the renewal fee due in respect of the year in which the mention of the grant of the European patent is published.

Note on payment of the designation fee(s):

If the designation fee(s) become(s) due after the communication under Rule 71(3) EPC, the mention of the grant of the European patent will not be published until the designation fee(s) has/have been paid (R. 71a(3) EPC).

4.1.2 After publication, the **European patent specification can be downloaded free of charge from the EPO publication server <https://data.epo.org/publication-server> or ordered from the Vienna sub-office upon payment of a fee (OJ EPO 2005, 126).**

Until 31 December 2013, each proprietor may request in writing to receive the certificate for the European patent together with one copy of the new patent specification only if the request is filed within three-month or

the additional two-month period (R. 95(3) and (4) EPC). If such request has been previously filed, it has to be confirmed within the same period. The requested copy is free of charge. Any request or confirmation of a request filed after 31 December 2013 or after expiry of these periods will not be dealt with and the certificate will be delivered without a copy of the new European patent specification (cf. Notice from the European Patent Office dated 16 July 2013 concerning communication of the certificate for a European patent, OJ 2013, 418).

4.1.3 Filing of translations in the Contracting States

As regards translation requirements prescribed by the Contracting States under Article 65(1) EPC, please consult the website of the European Patent Office

www.epo.org → Law & practice → Legal texts, National law relating to the EPC

www.epo.org → Law & practice → All Legal texts → London Agreement

In the case of a valid extension or validation

As regards translation requirements prescribed by the Extension or or Validation States, please consult the website of the European Patent Office

www.epo.org → Law & practice → Legal texts, National law relating to the EPC

Failure to supply a prescribed translation in a Contracting State, or in an Extension or Validation State may result in the patent being deemed to be void *ab initio* in the State concerned (Art. 65(3) EPC).

4.2 In case of 2.2 above

If the present communication under Rule 71(3) EPC is based on an auxiliary request and, within the time limit, you maintain the main request or a higher ranking request which is not allowable, the application will be refused (Art. 97(2) EPC).

If the Examining Division gives its consent to the requested amendments or corrections, it will issue a new communication under Rule 71(3) EPC; otherwise, it shall resume the examination proceedings (R. 71(6) EPC).

5. Filing of a divisional application

Any divisional application relating to this European patent application must be filed directly with the European Patent Office in Munich, The Hague or Berlin and will be in the language of the proceedings for the present application, or if the latter was not in an official language of the EPO, the divisional application may be filed in the language of the present application as filed (see Article 76(1) and Rule 36(2) EPC). Any such divisional application must be filed while the present application is still pending and the time limit for filing divisional applications must be observed (R. 36(1) EPC; Guidelines A-IV, 1.1.1).

6. Important notes concerning fee payments

6.1 For all payments, please refer to the relevant fee code(s).

6.2 Automatic debiting procedure

The fee for grant, including the fee for publication, and any additional claims fees due under Rule 71(4) EPC will be debited automatically on the date of filing of the translations of the claims, or on the last day of the period of this communication. However, if the designation fee(s) become(s) due as set out in Rule 71a(3) EPC and/or a renewal fee becomes due as set out in Rule 71a(4) EPC, these should be paid separately by another permitted way of payment in order not to delay the publication of the mention of the grant. The same applies in these circumstances to the payment of extension fees. For further details see the Arrangements for the automatic debiting procedure (AAD) and accompanying information from the EPO concerning the automatic debiting procedure (Annexes A.1 and A.2 to the Arrangements for deposit accounts (ADA) in Supplementary publication 4 - OJ EPO 2014).

6.3 Important information relating to fee amounts

Following any amendment to the Rules relating to Fees, the amount(s) mentioned in this communication may be different from the amount(s) **actually due on the date of payment**. The latest version of the Schedule of fees and expenses, published as a Supplement to the Official Journal of the EPO, is also available on the EPO website (www.epo.org) and can be found under www.epo.org/schedule-of-fees, which allows the viewing, downloading and searching for individual fee amounts, both current and previous.

Please note that procedural fees are usually adjusted every two years, on even years, with effect from 1 April.

- 6.4 **Payments by cheque** delivered or sent direct to the EPO are no longer accepted as from 1 April 2008 (see OJ EPO 2007, 626).

Examining Division:

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Enclosure(s): Text intended for grant (206 pages)

EPO Form 2056
EPO Form 2906