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Datasheet for the decision of 30 November 2018

Case Number: T 0102/13 - 3.3.08

Application Number: 02727397.8

Publication Number: 1379625

IPC: C12N5/07

Language of the proceedings: EN

Title of invention:
CD4+CD25+ REGULATORY T CELLS FROM HUMAN BLOOD

Patent Proprietor:
Argos Therapeutics, Inc.

Opponent:
Miltenyi Biotec GmbH

Headword:
Human Tregs/ARGOS THERAPEUTICS

Relevant legal provisions:
EPC Art. 54, 56, 100(a), 100(b)
RPBA Art. 12(4)

Keyword:
Patent as granted - sufficiency of disclosure (yes)
Novelty (yes)
Inventive step (yes)

Decisions cited:
T 0803/01

Catchword:

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Beschwerdekammern

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Case Number: T 0102/13 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 30 November 2018

Appellant I: (Patent Proprietor)	Argos Therapeutics, Inc. 4233 Technology Drive Durham, NC 27704 (US)
Representative:	Helbing, Jörg dompatent von Kreisler Selting Werner - Partnerschaft von Patent- und Rechtsanwälten mbB Deichmannhaus am Dom Bahnhofsvorplatz 1 50667 Köln (DE)
Appellant II: (Opponent)	Miltenyi Biotec GmbH Friedrich-Ebert-Str 68 51429 Bergisch-Gladbach (DE)
Representative:	Kisters, Michael Marcus Patentanwalt Miltenyi Biotec GmbH Corporate Legal Department Friedrich-Ebert Strasse 68 51429 Bergisch Gladbach (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 14 November 2012 concerning maintenance of the European Patent No. 1379625 in amended form.**

Composition of the Board:

Chairman	B. Stolz
Members:	M. R. Vega Laso
	D. Rogers

Summary of Facts and Submissions

I. European patent No. 1 379 625 with the title "$CD4^+CD25^+$ regulatory T cells from human blood" was granted from European patent application No. 02727397.8 which was filed under the Patent Cooperation Treaty and published as WO 02/072799 (in the following "the application as filed").

II. The patent was opposed on the grounds for opposition of Article 100(a) in conjunction with Articles 54 and 56, and Article 100(b) EPC.

III. In an interlocutory decision posted on 14 November 2012, an opposition division found that the ground for opposition of Article 100(b) EPC prejudiced the maintenance of the patent as granted (main request), but that the patent could be maintained on the basis of the claims according to the first auxiliary request then on file and the description adapted thereto.

IV. Claims 1 and 8 to 12 of the patent as granted read as follows:

"1. A pharmaceutical composition comprising

(a) suppressive and/or regulative human $CD4^+$ $CD25^+$ CTLA-4^+ T cells that are non-proliferative to stimulations via their TCR, but the anergic state being partially reversed by IL-2 and IL-15;

(b) expanded human $CD4^+$ $CD25^+$ CTLA-4^+ T cells that are obtainable by a method comprising stimulating the cells of (a) with a T cell stimulating agent or with antigen-presenting cells *ex vivo*;

(c) fixated $CD4^+$ $CD25^+$ CTLA-4^+ T cells that are obtained by *ex vivo* treatment of expanded human

$CD4^+$ $CD25^+$ CTLA-4^+ T cells of (b) with para-formaldehyde; or
(d) $CD4^+$ $CD25^+$ CTLA-4^+ T cells having a particular desired antigen-specific T cell receptor that are obtainable by activating/stimulating/expanding the $CD4^+$ $CD25^+$ CTLA-4^+ T cells of (a) with antigen presenting cells selected from immature or mature dendritic cells (DC) presenting said antigen *in vitro* or by utilizing a ligand/antibody to a particular T cell receptor expressed on (subsets of) $CD4^+$ $CD25^+$ CTLA-4^+ regulatory T cells, or a MHC-peptide complex binding to a particular T cell receptor, on (subsets of) $CD4^+$ $CD25^+$ CTLA-4^+ T cells, or by transfection of a T cell receptor of desired antigen specificity into the *ex vivo* isolated or expanded T cells of (a) or (b).

8. The method of claim 7, wherein the T cell stimulating agent is a composition comprising:

(a) anti-CD3 and/or anti-CD28 ligands/monoclonal antibodies;
(b) a ligand/antibody to T cell receptors on the surface of $CD4^+$ $CD25^+$ CTLA-4^+ T cells or to T cell receptor components; or
(c) MHC-peptide complexes binding to the T cell receptors expressed on the surface of regulatory T cells; or
(d) a phorbolester and a calcium ionophor.

9. The method of claim 8, wherein the T-cell stimulating agent is a composition comprising superagonistic antibodies.

10. The method of claim 7, wherein the antigen-presenting cells are selected from autologous cells,

non-autologous cells, and artificial antigen-presenting cells.

11. The method of claim 10, wherein the antigen-presenting cells are dendritic cells.

12. A method to identify, monitor and/or remove suppressive and/or regulative human $CD4^+$ $CD25^+$ CTLA-4^+ T cells, which are non-proliferative to stimulations via their TCR, but the anergic state being partially reversed by IL-2 and IL-15, from human blood and other tissues *ex vivo*, which method comprises:

(a) utilizing agents/ligands specifically binding to the CD4 and, CD25, and/or CTLA-4 (CD152) entities on the T cells; and/or
(b) utilizing immunoadsorption methods; and/or
(c) utilizing a stimulating agent as defined in claim 8 or 9 or antigen presenting cells as defined in claim 10 or 11."

Dependent claims 2 and 3 are directed to embodiments of the pharmaceutical composition of claim 1. Independent claim 4 is directed to suppressive and/or regulative human $CD4^+$ $CD25^+$ CTLA-4^+ T cells, expanded human $CD4^+$ $CD25^+$ CTLA-4^+ T cells, fixated $CD4^+$ $CD25^+$ CTLA-4^+ T cells, or $CD4^+$ $CD25^+$ CTLA-4^+ T cells having a particular desired antigen-specific T cell receptor as defined in claim 1 or 2 for use in adoptive transfer therapy, for use in treating autoimmune diseases, or for use in preventing/treating transplantation reactions including graft versus host disease and graft rejections. Claims 5 and 6 concern the use of cells as specified in claim 4 for preparing various types of medicaments. Independent claim 7 relates to a method for expanding suppressive and/or regulative human $CD4^+$

$CD25^+$ $CTLA\text{-}4^+$ T cells as defined in claim 1(a). Dependent claim 13 defines an embodiment of the method of claim 12. Independent claim 14 is directed to various uses of the cells defined in claim 1 or 2. Claims 15 and 16 relate to *ex-vivo* methods for preparing $CD4^+$ $CD25^+$ $CTLA\text{-}4^+$ T cells with a particular desired antigen-specific T cell receptor. Claim 17 concerns $CD4^+$ $CD25^+$ $CTLA\text{-}4^+$ T cells having a particular desired antigen-specific T cell receptor.

V. The patent proprietor and the opponent (appellant I and appellant II, respectively) both filed appeals against the interlocutory decision and submitted a statement setting out the grounds of appeal. Together with its statement of grounds, appellant II submitted new evidence.

VI. Each party replied to the statement of grounds of the other party. Together with its reply, appellant I filed further evidence. Appellant II submitted further observations on appellant I's reply.

VII. Both parties requested oral proceedings as a subsidiary request.

VIII. The parties were summoned to oral proceedings before the board. In a communication sent in preparation of the oral proceedings, the board expressed its provisional opinion on various procedural and substantive issues relevant to the case.

IX. Oral proceedings were held on 30 November 2018.

X. The following documents are referred to in this decision:

(1): T. Takahashi *et al.*, 1998, International Immunology, Vol. 10, No. 12, pages 1969 to 1980;

(2): H. Kanegane *et al.*, 1991, International Immunology, Vol. 3, No. 12, pages 1349 to 1356;

(3): L.S. Taams *et al.*, December 2000, Annual Congress of the British Society of Immunology, Abstract IS6;

(4): W.F. Ng and R.I. Lechler., December 2000, Annual Congress of the British Society of Immunology, Abstract 3.12;

(5): A. Koulis and D. Robinson, February 2001, J. Allergy Clin. Immunol., Abstract 966;

(17): M. Miyara and S. Sakaguchi, 2011, Immunology and Cell Biology, Vol. 89, pages 346 to 351;

(19): L.S. Taams *et al.*, 2001, Eur. J. Immunol., Vol. 31, pages 1122 to 1131;

(28): Wikipedia entry "Cluster of differentiation", undated; and

(31): F. Powrie, 2001, Diabetes/Metabolism Research and Reviews, Vol. 17, Suppl. 1, page S15.

XI. The submissions made by appellant I concerning issues relevant to this decision, were essentially as follows:

Main request – patent as granted

Article 100(b) EPC – claims 12 and 13

The opposition division erred in finding that the variant (a) of the method according to claim 12 could not be reproduced by the skilled person. Contrary to the opposition division's view, the use of a ligand that specifically binds to the CTLA-4 (CD152) entity was not necessary, especially if starting from cell populations that were high in CTLA-4 as shown in Example 1 of the patent. No experimental evidence had been brought forward showing that the claimed method could not be carried out without the use of a CTLA-4 ligand. In fact, appellant II commercialized applications for isolating human regulatory T cells (Tregs) from peripheral blood using ligands that specifically bind only to CD25 and CD4.

The objection of lack of sufficient disclosure concerning the variants (b) and (c) of the method of claim 12 was not justified. The patent specification included several working examples in which the natural Tregs were monitored for their phenotype and/or behaviour, including the characterization of expression of CTLA-4 in the cells following stimulation (see, e.g., Figure 1C) and the cells' ability, when stimulated via the TCR, to suppress the activation of other T cells (see, e.g., Example 3).

Articles 100(a) and 54 EPC

Claims 1 to 6

Document (2) did not make available to the public suppressive and/or regulatory human $CD4^+$ $CD25^+$ $CTLA\text{-}4^+$

T cells. Although human T cells exhibiting the $CD4^+$ $CD25^+$ phenotype were described in this document, they were said to represent a novel transitional population in the maturation process of naïve into *memory* $CD4^+$ cells. The properties of the cell population described in document (2) differed from those of the T cells comprised in the pharmaceutical composition of the invention. Moreover, document (2) did not describe or even suggest a pharmaceutical use of the cells described therein. Thus, the subject-matter of claims 1 to 6 was novel over the content of document (2).

Claim 12

Also the subject-matter of claim 12 was novel. Document (3) mentioned that the cell population described therein expressed CTLA-4, but, as is apparent from document (19), CTLA-4 expression in that population was only intracellular. Documents (4) and (5) did not even mention CTLA-4 expression.

Articles 100(a) and 56 EPC

Claims 1 to 6

Document (3) as the closest state of the art

Document (3) did not describe how to isolate human suppressive and/or regulatory $CD4^+$ $CD25^+$ $CTLA\text{-}4^+$ T cells nor any use for them. It was also unclear whether the T cells described therein were Tregs. Human Tregs were characterized by a $CD4^+$ $CD25^+$ phenotype and also by *constitutive* expression of CTLA-4. Because of the differences between the immune system of man and mice, the available knowledge on murine Tregs could not be automatically transferred to the isolation of the

human counterparts. A person skilled in the art could not have reasonably expected to isolate human Tregs following the method described in document (1).

Document (1) as the closest state of the art

Document (1) related to murine Tregs. At the priority date, a person skilled in the art could not reliably predict which attributes of the murine Tregs would be found in human Tregs, should they exist. In fact, there were significant differences between murine and human Tregs. For instance, in contrast to the situation in mice, where most $CD4^+$ $CD25^+$ T cells were suppressive Tregs, in humans only those $CD4^+$ $CD25^+$ T cells with the very highest levels of CD25 expression were suppressive; the bulk of human $CD4^+$ $CD25^+$ T cells were simply activated effector T cells. Thus, an antibody specific for CD25 would bind not only human Tregs, but also human effector T cells. Document (3) did not make available any method to isolate Tregs. By combining the teachings of documents (1) and (3), the skilled person would not have obtained human Tregs as comprised in the pharmaceutical composition of claim 1.

Claim 12

Document (3) did not describe any method for the isolation of a suppressive $CD4^+$ $CD25^+$ CTLA-4^+ T cell population. A person skilled in the art trying to obtain such cells performing the method described in document (5) for isolating human $CD4^+$ $CD25^+$ T lymphocytes, would not have identified a Tregs population as defined in claim 12.

XII. The submissions by appellant II, insofar as they are relevant to the present decision, may be summarised as follows:

Main request – patent as granted

Article 100(b) EPC – claims 12 and 13

The opposition division had been mistaken about the meaning of the "+" or "-" symbol used in the claims for defining the suppressive T cells. As is apparent from document (28), these symbols indicated whether the cells expressed or lacked a certain marker. However, they did not define whether the marker was expressed intracellularly or on the cell surface. Hence, a cell population characterized as being $CD4^+$ $CD25^+$ CTLA-4^+ included not only cells having those markers on the cell surface, but also cells expressing them intracellularly. The specification did not teach how intracellular markers could be identified without lysing the cells. It was apparent from Example 2 of the patent (page 9, lines 44 and 45) that the suppressive T cells expressed CTLA-4 on the surface only transiently. Since the claims did not specify the timing of surface expression, a person skilled in the art could not carry out the claimed method without undue burden.

Variants (b) and (c) of the method of claim 12 did not refer to the cell features specified in the preamble. Hence, the person skilled in the art was left in the dark as to which methods known in the art he/she could use for identifying, monitoring and/or removing the suppressive and/or regulatory T cells. Variant (c) involved the use of stimulating agents or antigen presenting cells. However, it could not be derived from

the specification how the desired cell population could be identified or removed only through stimulation. The scope of claims 12 and 13 could not be clearly determined and the claimed invention could not be carried out without undue burden.

Articles 100(a) and 54 EPC

Claims 1 to 6

The subject-matter of claims 1 to 6 lacked novelty in view of document (2) which described $CD4^+$ $CD25^+$ T cells. According to decision T 803/01 of 9 September 2003, novelty of a pharmaceutical composition could not be established only on the basis of a higher degree of purity of one of its components. As is apparent from Figure 1B of the patent, 73% of the cells in a $CD4^+$ $CD25^+$ population expressed the CTLA-4^+ marker, i.e. $CD4^+$ $CD25^+$ CTLA-4^+ T cells were a subpopulation of $CD4^+$ $CD25^+$ T cells. Hence, the sole difference between the composition of claim 1 and the cell population described in document (2) was the degree of purity of one of its cell components. Even though document (2) did not mention CTLA-4^+ as a marker, this feature was inherent. The use of the composition for pharmaceutical purposes was derivable from the sentence bridging the left and right-hand columns on page 1355 of document (2). At the priority date, it was well known that $CD4^+$ $CD25^+$ T cells played a central role in the immune response.

Claim 12

Document (3) described $CD4^+$ $CD25^+$ CTLA-4^+ T cells. While this document did not provide a method to identify them, it was immediately apparent to a person

skilled in the art applying his/her common general knowledge that this could be done using ligands that bind the markers. The same applied as regarded documents (4) and (5). Hence, the subject-matter of claim 12 lacked novelty.

Articles 100(a) and 56 EPC

Claims 1 to 6

Document (3) as the closest state of the art

Starting from document (3), the problem to be solved was to find a use for the T cells described therein. For this purpose, it was obvious to a person skilled in the art to resort to document (1) which described methods for isolating murine suppressive T cells. Hence, the subject-matter of claims 1 to 6 lacked an inventive step.

Document (1) as the closest state of the art

Starting from document (1), which described murine Tregs, the problem to be solved was to find the human counterparts. Since the human and the murine immune system were similar, and the existence of such cells was described in document (3), the skilled person had a reasonable expectation of success. It was known from the mouse model that Tregs could be used to treat immune diseases. Thus, the subject-matter of claim 1 did not involve an inventive step in view of a combination of documents (1) and (3).

Claim 12

Starting from document (3), the problem to be solved was to provide suitable methods to isolate the T cells described therein. A method according to claim 12(a) was obvious in view of document (5). Having regard to the common general knowledge of the skilled person at the relevant date, also the methods of claim 12(b) and (c) did not involve an inventive step.

XIII. Appellant I (patent proprietor) requested that the decision under appeal be set aside and the patent be maintained as granted.

XIV. Appellant II (opponent) requested that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

Admission of document (31) into the proceedings

1. Document (31) was submitted by appellant II together with its statement of grounds of appeal, purportedly as evidence that at the priority date it was known that the immunological situation as regards suppressive T cells is essentially identical in mice and humans. In its communication in preparation of the oral proceedings, the board observed that it was not aware of any circumstances that might have prevented appellant II from filing document (31) in opposition proceedings, as the argument it purportedly supported was put forward early in those proceedings. Appellant II did not put forward any arguments that justified the late filing. Hence, the board, exercising the discretion conferred by Article 12(4) of the Rules

of Procedure of the Boards of Appeal, decided not to admit document (31) into the appeal proceedings.

Main request – patent as granted

Article 100(b) EPC – claims 12 and 13

2. In the decision under appeal, Article 100(b) EPC was found to prejudice the maintenance of the patent as granted. The opposition division held that a particular embodiment of the method defined in claim 12(a) in which suppressive and/or regulatory human $CD4^+$ $CD25^+$ $CTLA\text{-}4^+$ T cells are identified and/or removed using agents/ligands specifically binding only to the CD4 and CD25 markers, was not sufficiently disclosed in the patent. In their view, unless a ligand binding CTLA-4 was used, a person skilled in the art could not identify and/or remove cells with the features specified in the preamble of the claim.

3. The board disagrees with this view. According to Example 1 of the patent in suit, a more than 95% pure population of human $CD4^+$ $CD25^+$ $CTLA\text{-}4^+$ T cells can be obtained using a magnetic-activated cell sorting (MACS) CD4 negative selection kit and afterwards a positive selection for CD25 (see paragraph [0023] and Figure 1A of the patent). The isolated cell population shows the characteristic features of suppressive T cells, in particular they exhibit a reduced proliferative response to both allogeneic and polyclonal stimulation (see paragraphs [0024] to [0026] of the patent), and suppress, when stimulated via the T cell receptor (TCR), the activation of $CD4^+$ and $CD8^+$ cells (see paragraph [0028]).

4. Appellant II argued that the population of cells defined in claim 12 included cells which expressed CTLA-4 intracellularly and/or transiently, and that a person skilled in the art could not discern whether or not the cells illustrated in the upper row of Figure 1C of the patent in suit fall within the scope of the claims.

5. This argument is not persuasive. Contrary to appellant II's view, in the present case the decisive question in the context of Article 100(b) EPC is not whether a particular cell population described in the patent falls within the scope of the claims, but rather whether the patent provides the skilled person with technical information and guidance sufficient to enable him/her to identify, monitor and/or remove, without undue burden, suppressive and/or regulatory human T cells as defined in the preamble of claim 12.

6. It has not been disputed by appellant II that cells isolated using the method disclosed in Example 1 of the patent are in fact suppressive and/or regulatory $CD4^+$ $CD25^+$ CTLA-4^+ T cells as defined in claim 12, and there is no evidence on file that the disclosed method can only be carried out with undue burden or applying inventive skills. Hence, the board must conclude that the technical information provided in Example 1 of the patent enables a person skilled in the art to identify the isolated cells as suppressive and/or regulatory human $CD4^+$ $CD25^+$ CTLA-4^+ T cells having the features specified in claim 12.

7. As regards appellant II's argument based on Figure 1C of the patent, the board remarks that the analysis of CTLA-4 expression shown in the upper row of this figure concerns a population of $CD4^+$ **$CD25^-$** T cells. Whether

and to which point of time this cell population expresses CTLA-4 is, in the board's view, immaterial in the context of assessing whether the claimed methods to identify, monitor and/or remove suppressive human $CD4^+$ **$CD25^+$** CTLA-4 T cells are sufficiently disclosed in the patent.

8. Also the arguments put forward by appellant II concerning the methods of claim 12(b) and (c) fail to persuade. The fact that in claim 12(b) and (c) the required markers are not mentioned might be seen as an issue under Article 84 EPC - which is not a ground for opposition -, but it is not prejudicial in the context of assessing sufficiency of disclosure. Since the relevant markers are disclosed in the patent, it is immediately apparent to a person skilled in the art seeking to identify, monitor and/or remove suppressive human $CD4^+$ $CD25^+$ CTLA-4 T cells using immunoadsorption methods which ligands are required. As for the methods according to claim 12(c), in which stimulating agents as defined in claim 8 or 9, or antigen presenting cells as defined in claim 10 or 11 are used, the patent as granted discloses in the passage from page 4, line 40 to page 5, line 2 ligands, stimulating agents and antigen-presenting cells suitable for carrying out the claimed methods. Appellant II neither disputed sufficiency of disclosure as regards the stimulating agents defined in claim 8 or 9, or the antigen presenting cells defined in claim 10 or 11, nor put forward any verifiable facts to substantiate its objection. Hence, the objection of lack of sufficient disclosure with respect to claim 12(b) and (c) fails.

9. For these reasons, the board concludes that, contrary to the findings in the decision under appeal,

Article 100(b) EPC does not prejudice the maintenance of the patent as granted.

Articles 100(a) and 54 EPC

Claims 1 to 6

10. In the decision under appeal, the opposition division found that the subject-matter of claim 1 of the first auxiliary request then on file, which was identical to claim 1 of the patent as granted, was not anticipated by either document (1) or document (2).

11. The finding on novelty over document (1) was not contested in appeal proceedings and the board sees no reason to question it. As regards document (2), the board shares the opposition division's view that a cell population as defined in claim 1 is not unambiguously disclosed in this document.

12. Document (2) describes $CD4^+$ $CD25^+$ T cells isolated from neonatal blood which are considered to "*... represent the novel transitional population in the maturation process of naïve into memory $CD4^+$ T cells*" (see last sentence of the Abstract). As stated in the decision under appeal, document (2) does not describe the isolated cell population as being CTLA-4^+, one of the markers that characterize the T cells comprised in the pharmaceutical composition of claim 1.

13. Appellant II contended that the presence of the CTLA-4^+ marker in the cell population of document (2) was inherent. This argument could however only be accepted if there were no doubt that the $CD4^+$ $CD25^+$ T cells of document (2) and the $CD4^+$ $CD25^+$ CTLA-4 T cells comprised in the pharmaceutical composition of claim 1

are the same T cell population. This was disputed by appellant I pointing to the passage on top of the left-hand column on page 1350 of document (2) which describes the ability of memory $CD4^+$ T cells to proliferate in response to sufficient amounts of exogenous IL-2, in contrast to the behaviour of the $CD4^+$ $CD25^+$ CTLA-4^+ T cells defined in claim 1. According to the patent, the anergic state of the latter cells is only **partially** reverted if high doses of IL-2 (500 U/ml) are combined with polyclonal activation by plate-bound anti-CD3 and anti-CD28 (see page 6, lines 15 to 19 and Figure 2D of the patent in suit). This difference in behaviour already casts doubts as to whether the two T cell populations are the same.

14. Moreover, there is no indication whatsoever in document (2) that the cell population described therein may have a suppressive and/or regulatory ability, i.e. the ability to prevent or regulate both the activation and the effector function of autoreactive T cells. Contrary to appellant II's view, in the absence of evidence characterizing the cells described in document (2) as CTLA-4^+ T cells, this functional feature of the T cells comprised in the pharmaceutical composition of the present invention, which is essential for the uses specified in claim 3, in fact delimits the claimed subject-matter against document (2).

15. Furthermore, a person skilled in the art cannot derive from document (2) the use of the T cell population described therein as a component of a pharmaceutical composition. The passage on page 1355 of document (2) on which appellant II relied reads as follows:

> "***Evaluation*** *of this population* [CD45RA$^+$ CD4$^+$ T cells expressing IL-2R α-chain (CD25)] *in some immunological diseases such as autoimmune diseases, virus-associated disorders, immune deficiency states, or bone marrow transplantation would illuminate the dynamics of development of naïve to memory T cells following antigenic stimulation*" (emphasis added by the board)

16. In this passage, the authors of document (2) suggest that, in order to elucidate the role that the cell population described therein plays in the development of naïve to memory T cells, its presence in various disease conditions affecting the immune system should be examined. In the board's view, these statements must be read as suggestions for further research to be carried out on the described T cell population, rather than as a suggestion - let alone a direct and unambiguous disclosure - of a pharmaceutical use of the cells.

17. For these reasons, novelty of the subject-matter of claim 1 of the patent as granted over document (2) must be acknowledged. The same applies, *mutatis mutandis*, to the subject-matter of claims 2 and 3, which depend on claim 1, as well as of claim 4 ("... *for use in treating autoimmune diseases ...*") and claims 5 and 6 ("*Use ... for preparing a regulatory medicament ... for treating autoimmune diseases ...*") because such uses of the cells defined in claim 1 are not derivable from document (2).

Claim 12

18. In the decision under appeal, the opposition division found that a person skilled in the art could not derive

directly and unambiguously from document (3) the method of claim 12 (see sections 5.2.3 and 5.2.4 of the decision).

19. While this finding was made in connection with the first auxiliary request then on file, it applies equally to claim 12 of the patent as granted. Like the opposition division, the board does not accept appellant II's argument that, even though document (3) does not describe a method as claimed in claim 12, the techniques specified in the claim, e.g. immunoadsorption methods, were widely used in the art at the relevant date. If this argument were accepted in the framework of assessing novelty, the boundary between the concepts of novelty and inventive step would be blurred. Hence, in the absence of an explicit description of a method as defined in claim 12 the content of document (3) cannot be considered to anticipate the subject-matter of this claim.

20. Documents (4) and (5), on which appellant II relied in appeal proceedings, neither characterize the $CD4^+$ $CD25^+$ T cell population(s) described therein as being $CTLA\text{-}4^+$, nor describe a method for the identification of the cells. Hence, also these documents cannot be regarded as prejudicial to the novelty of the method of claim 12.

21. For these reasons, appellant II's objection of lack of novelty fails.

Articles 100(a) and 56 EPC

Document (3) as the closest state of the art

22. In the decision under appeal, the opposition division found that document (3) represented the closest state of the art. This document describes human $CD4^+$ $CD25^+$ T cells that express CTLA-4, are anergic and suppress the proliferative activity of $CD4^+$ $CD25^-$ T cells. In the view of the opposition division, document (3) did not describe unambiguously a T cell population as defined in claim 1, because it was not clear whether CTLA-4 was expressed intracellularly or whether it was a surface marker. Consequently, the problem to be solved had to be formulated as the provision of a further population of suppressive T cells or, alternatively, the further characterization of human $CD4^+$ $CD25^+$ T cells. Since document (3), either alone or combined with other documents on file or the common general knowledge, gave no hint towards a cell population with CTLA-4 as surface marker, the present invention was not obvious to the skilled person (see section 6.7 of the decision).

23. It is undisputed that document (3), which is a short abstract of experimental results presented at the Annual Congress of the British Society of Immunology, does not describe a pharmaceutical composition. Like the opposition division, the board is not persuaded that a person skilled in the art can unambiguously derive from document (3) a suppressive and/or regulatory human T cell population as described in the patent and comprised in the pharmaceutical composition of claim 1, in particular as regards the constitutive expression of CTLA-4 as a surface marker. Appellant II did not dispute that there are different populations of

human suppressive $CD4^+$ $CD25^+$ T cells, nor put forward any evidence that, in spite of uncertainties as regards the expression of CTLA-4, the suppressive T cell population described in document (3) and that in the patent in suit are the same.

24. Under these circumstances, whether a person skilled in the art starting from document (3) and seeking a use for the human T cell population described therein, would arrive at a pharmaceutical composition as defined in claim 1 cannot be ascertained. The same applies if, as appellant II argued, the teaching of document (3) is combined with that of document (1) which describes only murine suppressive $CD25^+$ $CD4^+$ T cells. Document (1) does not include any information on human suppressive and/or regulatory T cells (Tregs) from which it could be derived that the suppressive T cell population described in document (3) and that comprised in the pharmaceutical composition of claim 1 are the same populations. It should be noted that document (1) does not even mention constitutive expression of CTLA-4 as a surface marker in murine suppressive T cells, let alone in their human counterparts.

25. The findings above apply equally, *mutatis mutandis*, to the compositions of dependent claims 2 and 3 and the medical uses of the human suppressive and/or regulative $CD4^+$ $CD25^+$ CTLA-4^+ T cells as defined in claims 4 to 6.

26. For these reasons, appellant II's objection that the subject-matter of claims 1 to 6 lacks an inventive step in view of document (3) combined with document (1) fails.

27. In the decision under appeal, the opposition division found that a combination of the teachings of

document (3) with those of other documents on file, or with the common general knowledge of the skilled person "*... did not lead in an obvious way to the subject-matter of claim 1 (or any of the other claims)*" (see section 6.8 of the decision). In appeal proceedings, no arguments have been put forward to substantiate the objection of lack of inventive step in view of a combination of document (3) with other documents, in particular documents (2), (4) and (5).

Document (1) as the closest state of the art

28. Document (1) is a scientific article which describes **murine** suppressive $CD25^+$ $CD4^+$ T cells. In the first paragraph under the heading "Introduction", reference is made to autoimmune diseases in human and animals, and possible mechanisms involving various subpopulations of T cells are discussed. In the last paragraph of the right-hand column on page 1978, it is stated:

> "*In conclusion, we have shown that naturally anergic and suppressive* [murine] *T cells are present in the normal immune system as a functionally and phenotypically distinct subpopulation of T cells and actively preventing autoimmune disease by suppressing activation/expansion of self-reactive T cells. Further analysis of this T cell-mediated mechanism of selftolerance would contribute to our understanding of the cause and mechanism of autoimmune disease and help in devising new strategies for treating or preventing it. Manipulation of the $CD25^+CD4^+$ T cell population would also make it possible to suppress or enhance immune responses to non-self antigens in general.*"

29. Starting from document (1), the problem to be solved is the provision of human Tregs and a pharmaceutical use thereof. In appeal proceedings, it was not disputed that this problem is solved by the pharmaceutical composition of claims 1 to 3 and the medical uses of the human suppressive and/or regulative $CD4^+$ $CD25^+$ $CTLA\text{-}4^+$ T cells as defined in claims 4 to 6.

30. In the light of the possible therapeutic applications of Tregs for the treatment or prevention of autoimmune diseases, there is no doubt that a person skilled in the art would try to isolate the human counterparts of the suppressive T cells described in document (1), and that he/she would hope to succeed. However, contrary to appellant II's view, the board is not persuaded that the fact that Tregs characterized by certain markers had been found in mice necessarily means that the same cells having the same markers existed in humans. While it is true that the murine and human immune systems show many similarities, they differ to some extent. In particular, as regards Tregs the post-published document (17), which was submitted by appellant I as expert evidence, shows an important difference in the expression of the $CD25^+$ marker between the murine and human cells. It is stated in this document that:

> "*... in contrast with murine $CD4^+$ $CD25^+$ Tregs, the majority of which are suppressive in vitro, only those $CD4^+$ T cells with the highest levels of CD25 expression are suppressive in human beings mainly because human $CD4^+$ $CD25^+$ T cells in the peripheral blood lymphocytes contain $CD25^+$-activated T cells*" (see page 347, right-hand column, lines 9 to 13 from the bottom)

31. It follows from these statements that, if a person skilled in the art at the priority date tried to isolate human Tregs from human peripheral blood following the teachings of document (1), i.e. using antibodies specific for the $CD4^+$ and $CD25^+$ markers described in document (1), he/she obtained not only Tregs, but also effector T cells which have no suppressive and/or regulatory ability. Thus, in order to identify the human suppressive T cells among the isolated human $CD4^+$ $CD25^+$ T cells the skilled person had to find further markers that distinguish the two T cell subpopulations.

32. Appellant II pointed to document (3), which describes an additional marker, CTLA-4, and argued that the skilled person combining the teachings of this document with those of document (1) would be able to isolate human Tregs as comprised in the pharmaceutical composition of claim 1, without applying any inventive skills. However, as stated above, document (3) is completely silent about the pattern of expression of CTLA-4. As illustrated in Figure 1C of the patent in suit, $CD4^+$ $CD25^-$ T cells, which become $CD25^+$ when activated, also express CTLA-4, but only transiently. Hence, in order to isolate human Tregs as comprised in the pharmaceutical composition of claim 1, a person skilled in the art had to identify $CD4^+$ $CD25^+$ T cells expressing CD25 at a high level and CTLA-4 constitutively.

33. Since neither document (1) nor document (3) or a combination of both gives the skilled person any hint to such an approach, an inventive step must be acknowledged for the subject-matter of claims 1 to 6.

Claim 12

34. Appellant II based its objection of lack of inventive step on a combination of the teachings of document (3) and (5). Document (3), which appellant II considered to be the closest state of the art, does not describe any method to identify human suppressive and/or regulatory T cells as defined in claim 12. Document (5) describes the use of microbeads and a MACS column to separate human mononuclear cells into CD25 enriched and CD25 partially depleted populations. It is stated in this document that the enrichment of $CD25^+$ cells was concomitantly an enrichment of $CD4^+$ T cells.

35. This line of argument fails. As stated in document (5), applying the method described therein the skilled person could identify an enriched $CD4^+$ $CD25^+$ T cell population. There is, however, no evidence that the enriched T cell population described in document (5) is a suppressive and/or regulative $CD4^+$ $CD25^+$ CTLA-4^+ T cell population as defined in claim 12 which expresses CTLA-4 constitutively. It is this essential piece of information, which is missing in both documents (3) and (5), but disclosed in the patent in suit, what allows the person skilled in the art to devise a method to identify, monitor and/or remove human Tregs as defined in claim 12(a).

36. The same applies, *mutatis mutandis*, as regards appellant II's objection concerning the methods defined in claim 12(b) and (c). There is no evidence on file showing that it was part of the common general knowledge at the priority date that a constitutive CTLA-4 expression is a characterizing feature of human Tregs. Consequently, also the objection of lack of

inventive step based on document (3) combined with the common general knowledge fails.

Conclusion

37. It follows from the above that Articles 100(a) and 100(b) EPC do not prejudice the maintenance of the patent as granted.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is maintained as granted.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated