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The European Patent Office
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Germany

4 April 2012

Dear Sirs

European Patent Application No. 09013687.0-2405
ONO PHARMACEUTICAL CO., LTD., et al
Our ref: N.108846A GCW/eg

In response to the Examination Report dated 24 November 2011, I attach a new Main Request and an Auxiliary Request. I also attach:

- a track-changes version of the previous claims showing the amendments which have been made to them to derive the Main Request;
- a track-changes version of the previous claims showing the amendments which have been made to them to derive the Auxiliary Request;
- an Annex which reports competitive binding experiments between the 5C4 antibody according to the present invention and four further monoclonal antibodies described in the present application (17D8, 2D3, 4H1 and 7D3).

Amendments

The new Main Request and the Auxiliary Request are identical except for claim 3. Claim 3 of the Main Request corresponds to claim 3 of the present application as originally filed. There is also basis for claim 3 in the paragraph bridging pages 29 and 30 of the description and especially at page 29 lines 27 to 29. There is basis for the claim in the original version of the parent application, i.e. in International Application Publication No. WO 2006/121168, at claims 8 and 12 and at page 29 lines 27 to 29.

Claim 3 of the Auxiliary Request corresponds to claim 3 previously on file except that new claim 3 refers to “PD-1 epitope” rather than to “PD-1”. Basis for that claim was set out in my letter of 17 August 2011 responding to the previous Examination Report. More specifically, basis for specifying that the antibody or antigen-binding

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portion thereof “*binds to the same PD-1 epitope as does the antibody of claim 1 or 2*” can be found at page 29 lines 26 and 27.

As regards the amendments which have been made both to the Main Request and to the Auxiliary Request:

- It has now been made clear in claim 1 that the abbreviation “PD-1” represents Programmed Death 1 protein. Basis for that change can be found in the first line of the “*Background of the Invention*” section on page 1 of the description.
- New claim 5 finds basis in the sentence bridging pages 58 and 59 of the description of both the present application as originally filed and of WO 2006/121168. Please also see Examples 3 and 4 and Figures 13 and 15. Example 3 and Figure 13A show that the 5C4 antibody according to the present invention binds to CHO cells whilst Example 4 and Figures 15A, B and C show that the 5C4 antibody binds to activated human T-cells, monkey PBMCs and transfected CHO cells.

Novelty

As a preliminary point, please note that Iwai *et al.*, Immunology Letters 83(3), 215-220, 2002 should be document D4. WO 2001/014557 was cited as document D3 in the Examination Report dated 8 April 2011.

In the Main Request, claim 3 has been amended to recite a “*monoclonal antibody, or antigen binding portion thereof, which cross-competes for binding to PD-1 with the antibody of claims 1 or 2*”. As mentioned above, support for this amended claim can be found in the specification in the paragraph spanning pages 29 and 30. This portion of the specification teaches that antibodies that have the ability to cross-compete for binding to PD-1 with the monoclonal antibody recited in claims 1 and 2 can be identified in standard PD-1 binding assays, e.g. BIAcore analysis, ELISA assays or flow cytometry, as described in the Examples. Further, Applicants submit herewith as an Annex data from competitive binding experiments which demonstrate that four monoclonal antibodies described in the present application (17D8, 2D3, 4H1 and 7D3) compete with antibody 5C4 according to claims 1 and 2 for binding to PD-1. Thus, the present application provides a genus of at least four antibodies that cross-compete for binding to PD-1 with the antibody of claims 1 or 2.

Applicants assert that new claim 3 of the Main Request is novel as they are unaware of, and the Examining Division has not cited, any prior art antibody that cross-competes with the structurally defined antibody of claim 1 or 2 for binding to PD-1.

Claim 3 of the Auxiliary Request specifies that the monoclonal antibody or antigen-binding portion thereof “*cross-competes for binding to the same PD-1 epitope as does the antibody of claim 1 or 2*”. As disclosed in the specification (see page 29, last paragraph), antibodies that bind to the same epitope on PD-1 have the ability to cross-compete for binding to PD-1. Thus, claim 3 of the Auxiliary Request is also fully supported by the application. Applicants are unaware of, and the Examining

Division has not identified, any prior art disclosing an antibody that binds to the same epitope on PD-1 as does the antibody of claim 1 or 2. Accordingly, Applicants maintain that this version of claim 3 is novel.

Clarity

Both claim 3 of the Main Request and claim 3 of the Auxiliary Request are clear and meet the requirements of Article 84 EPC. Both versions of claim 3 include all essential features. Both versions satisfy the two-part test that is set out in the Examination Guidelines C-III-4.10 (previously C-III-4.7) for a claim which defines an invention by a result to be achieved.

Section C-III-4.10 of the Examination Guidelines states that a claim which attempts to define an invention by a result to be achieved may be allowed if:

- (i) the invention can only be defined in such terms or cannot otherwise be defined more precisely without unduly restricting the scope of the claims, and
- (ii) if the result is one which can be directly and positively verified by tests or procedures adequately specified in the description or known to the person skilled in the art and which do not require undue experimentation.

In the present instance, part (i) of the test is satisfied because it would unduly restrict the scope of claim 3 of either the Main Request or the Auxiliary Request if the claim had to be limited further, for example on the basis of particular sequence information. Also, part (ii) of the test is satisfied for both versions of claim 3 because, in each instance, the result specified in the claim can indeed be directly and positively verified by tests and procedures that are specified in the application and known in the art. These testing procedures do not require undue experimentation.

Claim 3 of the Main Request specifies that the antibody cross-competes for binding to PD-1 with the antibody of claim 1 or 2. As mentioned above, the paragraph spanning pages 29 and 30 of the description explains how antibodies that have the ability to cross-compete for binding to PD-1 with a monoclonal antibody as defined in claims 1 and 2 can be identified by standard PD-1 binding assays such as BIAcore analysis, ELISA assays or flow cytometry. Please see too the Examples of the present application. Corresponding comments apply in respect of claim 3 of the Auxiliary Request, which indicates that the monoclonal antibody or antigen binding portion thereof binds to the same PD-1 epitope as the antibody of claim 1 or 2. Thus, a skilled person would require the application of no more than routine experimentation to verify whether or not an antibody fell within the scope of either version of claim 3. Both versions of claim 3 are therefore allowable.

As regards the designation “PD-1”, this has now been clarified in claim 1. Claim 3 refers back to claim 1 directly and via claim 2. In fact, the designation “PD-1” is not an internal arbitrary designation. Rather, it is a term which would be well understood by a person skilled in the art as meaning Programmed Death 1 protein.

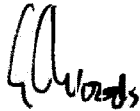
That is evident from the cited references D1, D3 and D4 and from the “*Background of the Invention*” section of the description.

Further Requests

The claims are now believed to be in allowable form and the Examiner is asked to reconsider them favourably. If however the Examiner has any further queries relating to the claims, I request that the Examiner issues a further Examination Report or telephones me. Only as a precaution in case the Examiner is minded to reject the application, I request Oral Proceedings.

I request an opportunity to revise the description to bring it into conformity with the claims. Also, I request that the Examiner telephones me or issues a further Examination Report if the Examining Division is minded to issue a Communication under Rule 71(3) EPC but wishes to propose amendments to the claims or to the description. The Applicants do not consent to modifications being made to the claims by the Examining Division without permission from the Applicants.

Yours faithfully



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ANNEX

Cross-competition between 5C4 and other HuMab anti-PD-1 mAbs

Experimental protocol

- Fig. 1 & 2 - CHO cells expressing Human PD-1 (CHO/PD-1) were incubated with 10 ug/ml of Fab fragment of 5C4 or hlgG1 for 30 minutes at 4 °C before addition of 4H1, 2D3 or 7D3 at a concentration of 0.2 ug/ml. Binding of 4H1, 2D3 or 7D3 to CHO/PD-1 cells were detected by fluorescent-conjugated goat anti-hlgG, Fc-gamma specific antibody.
- Fig. 3 - CHO cells expressing Human PD-1 (CHO/PD-1) were incubated with 10 ug/ml of 5C4 or hlgG1 for 30 minutes at 4 °C before addition of FITC-labeled 17D8.

Cross-competition between 5C4 and other HuMab anti-PD-1 mAbs

Fig. 1

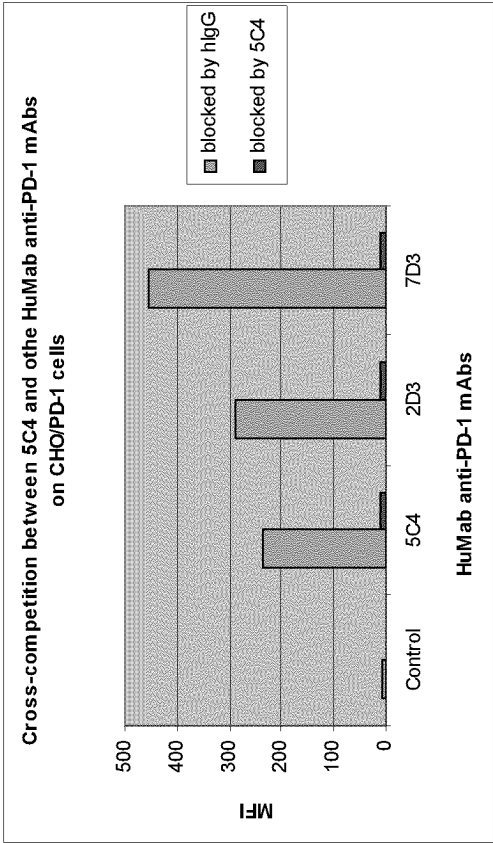


Fig. 2

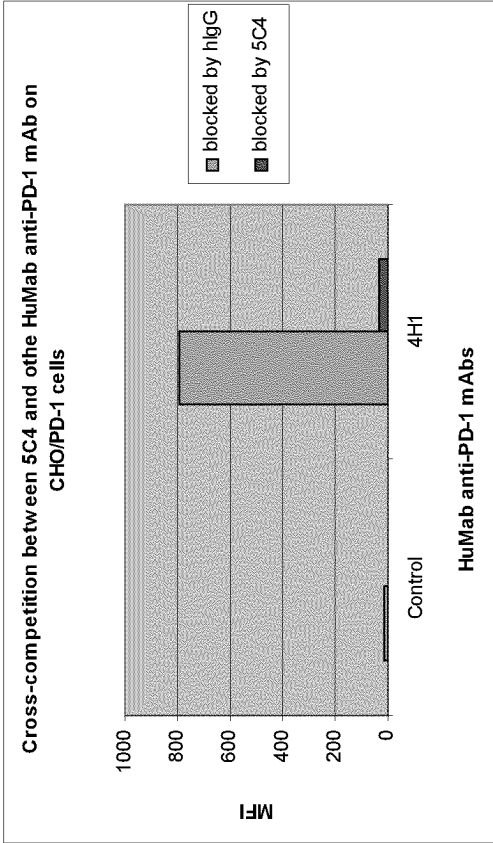


Fig. 3

