

**EUROPEAN PATENT 2161336**  
**ONO PHARMACEUTICAL CO., LTD. & MEDAREX, INC.**  
**ARGUMENTS IN SUPPORT OF OPPOSITION**

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**1. INTRODUCTION AND REQUESTS**

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- 1.1. European Patent 2161336, granted from EP-09013687.0, is opposed by Novartis AG under Article 99 EPC and Rule 76 EPC, as set out in the enclosed form 2300. Opposition is made to the extent of all claims for all designated states.
- 1.2. The documents relied upon in the opposition are listed in section 6 on page 7. Documents D1 to D5 were cited by the EPO already during search and examination and further copies are not filed. Documents D6 and D7 are newly cited. The Opponent reserves the right to rely additionally upon other documents cited in the Patent itself, and documents filed in the opposition proceedings by any other Opponent(s) or by the Patentee.
- 1.3. Opposition is made under Article 100(a) EPC because the claimed invention lacks novelty and inventive step. Opposition is also made under Article 100(b) because the Patent does not disclose the invention in a manner sufficiently clear or complete for it to be performed by a skilled person. Opposition is also made under Article 100(c) because the subject-matter of the Patent extends beyond the content of the application as filed and the parent application as filed. Briefly:
- Claim 3 and its dependent claims **lack novelty** over the PD1-17 antibody described by D6.
  - Any novel modification to the PD1-17 antibody must be trivial and **obvious**.
  - The lack of technical disclosure in the Patent creates a **lack of sufficient disclosure** for any modification to the PD1-17 antibody that is not obvious.
  - A number of the claims **add matter** over the parent application as filed.
- 1.4. The Opponent therefore requests revocation of the Patent as a whole under Article 101(2) EPC. If the Opposition Division will not grant this request on the basis of the written proceedings, the Opponent requests oral proceedings under Article 116 EPC.

**2. NOVELTY**

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**Claim 3 lacks novelty over antibody PD1-17 in D6**

- 2.1. D6, entitled “Antibodies against PD-1 and uses therefor”, discloses antibodies that specifically bind to PD-1, including human PD-1 (see D6, page 3 lines 10 to 11). These antibodies are stated to be useful in therapy, for example the treatment of cancer (page 25 line 12, page 42 line 11).
- 2.2. The antibodies of D6 are defined by their CDR sequences and their heavy and light chain variable region sequences. The CDR and variable region sequences of the

monoclonal antibody named “PD1-17” are disclosed in Table 1 (on page 11) of D6. This antibody has a light chain variable region of SEQ ID No.4 and a heavy chain variable region of SEQ ID No.2. Page 10 lines 22 to 23 and Example 1 on page 33 line 24 *et seq* of D6 recite that these variable regions were identified from a human scFv phagemid library. The human scFv domain comprising SEQ ID Nos. 2 and 4 is therefore an “antigen binding portion” (according to the definition at paragraph [027] of the Patent). Page 12 lines 15 to 17 and Example 5 on page 37 *et seq* of D6 recite that the scFv domain is converted to a (full-length) IgG antibody by the inclusion of human constant domains.

- 2.3. The PD1-17 human IgG antibody of D6 is therefore a monoclonal antibody that binds to human PD-1, and the PD1-17 scFv fragment is an antigen binding portion thereof. To anticipate claim 3, the PD1-17 antibody simply needs to cross-compete for binding to PD-1 with the antibody of claim 1 or claim 2 of the Patent.
- 2.4. D7 tests the binding properties of the PD1-17 antibody. Paragraph 9 of D7 confirms that the human monoclonal **PD1-17 antibody cross-competes with the 5C4 antibody of claim 1** (of the Patent) for binding to human PD-1, as determined by a **flow cytometry** assay. This type of assay is stated at page 14 line 3 of the Patent to be suitable for demonstrating cross-competition.
- 2.5. D7 also provides the results of a **second assay demonstrating cross-competition** between PD1-17 and 5C4; this second assay is a Biacore assay, which is also stated at page 14 line 3 of the Patent to be suitable for demonstrating cross-competition between two antibodies. Paragraph 15 of D7 confirms that the **5C4 antibody inhibits binding of PD1-17** to human PD-1 because **PD1-17 binds to the same epitope on human PD-1 as 5C4**.
- 2.6. The PD1-17 antibody of D6 thereby anticipates claim 3 because it cross-competes for binding to PD-1 with the 5C4 antibody of claim 1.

**Claims referring back to claim 3 also lack novelty**

- 2.7. D7, paragraphs 7 to 9 demonstrate that the PD1-17 antibody binds to human PD-1 expressed on a cell surface. Examples 8 and 9 of D6 also describe the use of PD1-17 to block PD-1 expressed on CD4<sup>+</sup> T cells. Accordingly, the PD1-17 antibody of D6 also anticipates claim 5.
- 2.8. Claims 6 to 8 recite inherent functional features of the antibody. These functions result from the antibody binding to PD-1. These inherent functional features do not distinguish the claimed antibody from the PD1-17 antibody, which binds to the same epitope on human PD-1 and will have the same function of blocking the receptor. Furthermore, Examples 8 and 9 (on pages 40 to 42) of D6 demonstrate that PD1-17 binding to PD-1 blocks a negative signal and thereby results in enhanced T cell proliferation. Example 10 of D6 goes on to disclose that this allows for modulation and augmentation of the immune response. There is nothing new in claims 6 to 8.

- 2.9. The IgG4 isotype, as recited in claim 9, is anticipated by paragraphs [036] and [043], and claim 8, of D6.
- 2.10. The pharmaceutical composition of claim 11 is anticipated by paragraph [095] and claim 11 of D6. Claim 12 is anticipated by the discussion of immunomodulation at paragraphs [076] to [079] and [0129] of D6, while claim 13 is anticipated by paragraphs [083] and [0129] of D6. Claims 14 and 15 of the Patent recite melanoma and prostate cancer and are therefore anticipated by the disclosure of these conditions at paragraph [083] of D6.
- 2.11. Claims 16 and 17 are anticipated by the disclosure of the treatment of infectious diseases in paragraph [012] of D6 and also by the disclosure of the treatment of infections with bacteria or viruses such as influenza or herpes, in paragraph [083] of D6.
- 2.12. D6 describes, at paragraph [063], linking the antibody to another functional molecule, e.g. another peptide or protein (e.g. antibody), a cytotoxin or a radioisotope. This anticipates the immunoconjugate of claims 18 to 23.
- 2.13. Claims 24 and 25 require that the antibody or binding portion is linked to a second functional moiety having a different binding specificity. This is anticipated both by the disclosure in paragraph [063] of D6 that the antibody can be linked to another antibody, and separately by the definition in paragraph [023] of D6 that the antibody can be polyspecific.

### **Priority**

- 2.14. D6 published before the earliest priority date and, in the interests of procedural efficiency, an examination of the priority claims is not necessary. However, the Opponent reserves the right to examine the Patentee's claims to a right of priority from the three US priority documents, should it become aware of an intervening document (published between one of the priority dates and the filing date) that is relevant to the validity of one or more of the claims.

## **3. INSUFFICIENCY**

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### **Insufficiency vs. Novelty**

- 3.1. If the Patentee would argue that the antibodies of claim 3 or any of its dependent claims are novel over the PD1-17 antibody then the Patent must be insufficient because it fails to provide any reliable way of distinguishing the claimed antibodies from the prior art antibody PD1-17. The specification does not teach the skilled person how to identify a genus of antibodies within the scope of claim 3 that does not include PD1-17.
- 3.2. Without any written or experimental guidance concerning how to distinguish prior art antibodies such as PD1-17 from an antibody within the scope of claim 3, the skilled person cannot test a critical parameter of the claim and this lack of disclosure contravenes Article 83 EPC.

### Insufficiency vs. Inventive Step

- 3.3. For completeness, if the Patentee would argue that the antibodies of claim 3 - likely amended to encompass a formally novel feature - are inventive, then such subject matter cannot be sufficiently described by the Patent.
- 3.4. It is well-established, for example according to T409/91, and as summarised by the Board in T189/09, that the scope of monopoly claimed must be:
- “... commensurate with and justified by the technical contribution made to the art”.*
- 3.5. The Patent provides no new technical teaching that could possibly justify a claim to a genus of antibodies, defined functionally, as in claim 3.
- 3.6. The Examples simply repeat the prior art knowledge that anti-PD1 antibodies can be isolated and used to modulate T cell proliferation; this is not a new teaching and does not enable anything that the Patentee might argue is unexpected. Any functionally-defined feature of an antibody (such as those recited in claims 3 to 10) that could not have been expected from the prior art also could not be plausibly expected to work based on the teaching of the Patent.
- 3.7. In the absence of any technical contribution, patent protection is not appropriate and the Patent therefore fails to meet the requirement of Article 83 EPC.

## **4. INVENTIVE STEP**

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- 4.1. The Examples in the Patent describe the identification of human monoclonal antibodies to PD-1. These antibodies were identified by immunising mice that express human antibody genes and creating hybridomas from the mice with the highest titers of anti-PD-1 antibodies. Seven clones were sequenced and analysed, and one of these – 5C4 – is the antibody now claimed in claims 1 and 2.
- 4.2. The Examples therefore describe an absolutely straightforward and standard method of producing antibodies.

### The antibody of claims 1 and 2 is an arbitrary alternative

- 4.3. The therapeutic utility of anti-PD-1 antibodies was well-known in the art, (see, for example, D1, D3 or D6). It is well established by the Boards of Appeal, that an inventive step can only be recognised for a further new antibody to a known target, if that antibody has unexpected effects, so that it is an *improvement* over the known antibodies (T735/00 and T645/02). There is no evidence in the Patent that the antibody of claims 1 and 2 is an improvement. Therefore, claims 1 and 2 define an antibody that is an arbitrary and non-inventive alternative to known antibodies, such as the PD1-17 antibody of D6.

### If claim 3 can be amended to confer novelty, it cannot be inventive

- 4.4. As explained in detail in section 2 above, the functionally-defined antibodies of claim 3 and many of its dependent claims lack novelty. There is no evidence in the Patent of a

surprising effect that is not provided by the prior art antibodies. Therefore, in the event that claim 3 is amended so that it is considered to be formally novel, then the novel feature must be a trivial modification of the novelty-destroying PD1-17 antibody. Such a trivial modification is not inventive.

- 4.5. It is wholly routine to produce and screen hybridomas expressing a monoclonal antibody, to identify an antibody with particular features. Such screening techniques are nothing out of the ordinary (T877/03, Reasons 23). For example, the identification of an antibody with a particular binding affinity for its target, or with a particular selectivity of binding, is entirely straightforward and obvious.
- 4.6. If the Patent's disclosure meets the requirements of Article 83 EPC for a genus of antibodies of the type defined by claim 3 then the invention would have been obvious from the prior art because the skilled person would have had a reasonable expectation that they could produce this genus of antibodies. In particular, the skilled person knew of the therapeutic utility of anti-PD1 antibodies and the task of finding further antibodies which would bind PD-1 required only routine work.
- 4.7. Therefore the claimed invention fails to meet the requirements of Article 56 EPC.

## **5. ADDED MATTER**

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- 5.1. Claims 3, 4, 6-8 and 10 extend beyond the content of the parent application (EP06746353.9/WO2006121168) as originally filed and therefore add matter, contrary to Article 76(1) EPC. Claim 5 was added during prosecution of the application as filed and creates combinations of features that are not disclosed in the application as filed, contrary to Article 123(2) EPC.

### **Claim 3**

- 5.2. Claim 3 is dependent upon claim 1 or claim 2. However, the Opponent can find no basis in the parent application as filed, for claim 3 when dependent upon claim 1, i.e. an antibody that cross-competes with an antibody defined only by the CDRs of SEQ ID Nos. 18, 25, 32, 39, 46 and 53. The corresponding claim in the parent application as filed (claim 8) only recites a reference antibody comprising the entire variable regions of SEQ ID No. 4 and SEQ ID No. 11; this definition of the reference antibody is also recited at page 3 lines 12 to 18 and at page 29 line 34 of the parent application as filed. Therefore, the combination of claim 3 with claim 1 is an intermediate generalisation that unallowably adds matter over the parent application as filed, contrary to Article 76(1) EPC.

### **Claim 4**

- 5.3. Claim 4 is directed to an antibody according to any one of claims 1 to 3, wherein the antibody (a) binds to human PD-1 with a  $K_D$  of  $5 \times 10^{-9}$  or less; **and** (b) binds to neither human ICOS, human CTLA-4 nor human CD28. This combination of features is not disclosed anywhere in the parent application as originally filed. The Patentee in the response dated 29th May 2009 (on the parent application) referred to the penultimate

paragraph at page 80 of the description as allegedly providing basis. However, this is a specific disclosure in Example 3 and is not generally applicable to all antibodies that cross-compete for binding to PD-1 with the antibody of claim 1 or 2, as required by granted claim 3. Hence the subject-matter of claim 4 also extends beyond the content of the parent application as originally filed.

**Claims 6 to 8 and 10**

- 5.4. During prosecution (on 29th May 2009) of the parent application, the Patentee stated that the claims corresponding to claims 6 to 8 and 10 of the Patent have basis in Examples 21, 18, 19 and 23/24, respectively, of the application as filed. However, these Examples are specific to the antibodies disclosed in each Example. The discussion in these Examples is not applicable to **all** antibodies that cross-compete for binding to PD-1 with the antibody of claim 1 or 2, as required by claim 3. In other words, the subject-matter of claims 6-8 and 10 as far as these claims refer back to claim 3 are an intermediate generalisation of disclosure only found in the Examples of the parent application as originally filed and therefore adds matter contrary to Article 76(1) EPC.
- 5.5. The unallowable generalisation provided by claims 6 to 10 is amplified by the presence of claim 5, which was added during prosecution of the application. Claim 5 is said by the Patentee to have basis in the single sentence bridging pages 58 and 59 of the description. Claims 6 to 8, and 10, depend in part from claim 5 and this dependency creates new combinations of features not present in the application as filed. For example, claim 8 when dependent upon claim 5 requires the *selection* of a single feature that has been *isolated* and *generalised* from Example 19 **and** the *combination* of this feature with the specific sentence spanning pages 58 and 59. This combination is not disclosed in the application as filed, and was made for the first time when claim 5 was added during prosecution. The new combinations of features, created by claims 6 to 8 and 10 when dependent upon claim 5, offend Article 123(2) EPC.
- 5.6. Claim 6 contains a further significant failing. The phrase “inhibits the suppression of CD4+ CD25- T cells by regulatory T cells”, in claim 6, is simply not present anywhere in the parent application as filed. Example 21 (at page 98 line 1) makes the very different statement that (emphasis added):
- “human monoclonal antibody 5C4 **partially released inhibition** imposed by Treg cells **on proliferation and IFN-gamma secretion** of CD4+ CD25- cells”,
- but this much more restrained description is not the same as the wording used in claim 6.
- 5.7. The phrase “enhances the antigen-specific memory response”, as used in claim 7, is also not present in the parent application as filed. Example 18, on which the Patentee relied during prosecution, refers much more generally to the provision of immunity to further tumour formation, while page 3 line 3 and page 16 line 9 describe not enhancement, but only the **stimulation** of antigen-specific memory responses. Antigen-specific **enhancement** is only described (e.g. at page 58 line 28) for the

combination therapy of antibody plus an antigen of interest, which is lacking from claim 7.

- 5.8. In summary, none of claims 3, 4, 6 to 8 and 10 find basis in the parent application as originally filed, and therefore these claims offend Article 76(1) EPC. The addition of claim 5 during prosecution offends Article 123(2) EPC, by adding matter over the application as filed.

## 6. CITATIONS

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### Cited during examination

- D1 Brown *et al.* (2003) *J Immunol* 170:1257-66.  
D2 Lonberg *et al.* (1994) *Nature* 368:856-859.  
D3 WO01/14557.  
D4 Iwai *et al.* (2002) *Immunol Lett* 83:215-220.  
D5 Brahmer *et al.* (2010) *J Clin Oncol* 28:3167-3175.

### Cited in this opposition

- D6 WO2004/056875.  
D7 Declaration from Dr. Jennifer Mataraza.