

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference see form PCT/ISA/220		FOR FURTHER ACTION See paragraph 2 below
International application No. PCT/EP2020/086600	International filing date (day/month/year) 17.12.2020	Priority date (day/month/year) 17.12.2019
International Patent Classification (IPC) or both national classification and IPC INV. C07K14/54 A61K38/00		
Applicant OSE IMMUNOTHERAPEUTICS		

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Griesinger, Irina Telephone No. +49 89 2399-0
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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- ☐ the entire international application
- ☒ claims Nos. 4(completely); 1, 5-24(partially)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- ☒ no international search report has been established for the whole application or for said claims Nos. 4(completely); 1, 5-24(partially)
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
 - ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).
- ☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 2, 3(completely); 1, 5-24(partially)

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement
- | | | |
|-------------------------------|-------------|---|
| Novelty (N) | Yes: Claims | <u>2, 3(completely); 1, 5-24(partially)</u> |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | |
| | No: Claims | <u>2, 3(completely); 1, 5-24(partially)</u> |
| Industrial applicability (IA) | Yes: Claims | <u>2, 3(completely); 1, 5-24(partially)</u> |
| | No: Claims | |
2. Citations and explanations
- see separate sheet**

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1 Application and cited documents

The application relates to an immunocytokine comprising an interleukin 7 (IL-7) variant linked to a binding moiety, preferably an Fc domain or to IgG1 or IgG4, said IL-7 variant being characterized by both reduced affinity for the IL-7 receptor and improved pharmacogenetics, wherein said effect is achieved by (i) the substitution of 4 cysteine residues by a serine residue or (ii) the substitution W142H/F/Y or (iii) the substitution D74E/Q/N or (iv) the substitution Q11E, Y12F, M17L, Q22E and/or K81R. Most of said substitutions decrease the affinity of IL-7 to its receptors CD127 and CD132 and thereby improve the pharmacokinetic properties, in particular the area under the curve (AUC) (example 1). Furthermore, it is shown that the combination of the IL-7 variant with known IgG1 or IgG4 variants enhance the biological activity of the IL-7 variants while conserving the pharmacogenetic properties (example 3).

The following documents are cited in the European search report.

- D1 WO 2006/061219 A2 (MERCK PATENT GMBH [DE]; GILLIES STEPHEN D [US]; WAY JEFFREY C [US]) 15 June 2006 (2006-06-15)
- D2 WO 2005/063820 A2 (MERCK PATENT GMBH [DE]; LAUDER SCOTT [US]; GILLIES STEPHEN D [US]) 14 July 2005 (2005-07-14)
- D3 WO 2008/003473 A2 (MERCK PATENT GMBH [DE]; GILLIES STEPHEN D [US]) 10 January 2008 (2008-01-10)
- D4 COSENZA L ET AL: "Disulfide bond assignment in human interleukin-7 by matrix-assisted laser desorption/ionization mass spectroscopy and site-directed cysteine to serine mutational analysis", JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY, US, vol. 272, no. 52, 26 December 1997 (1997-12-26), pages 32995-33000, XP002226701
- D5 THOMAS LIST ET AL: "Immunocytokines: a review of molecules in clinical development for cancer therapy", CLINICAL PHARMACOLOGY: ADVANCES AND APPLICATIONS, 1 August 2013 (2013-08-01), page 29, XP055289369, DOI: 10.2147/CPAA.S49231

- D6 STROHL ET AL: "Optimization of Fc-mediated effector functions of monoclonal antibodies", CURRENT OPINION IN BIOTECHNOLOGY, LONDON, GB, vol. 20, no. 6, 1 December 2009 (2009-12-01), pages 685-691, XP026778879
- D7 LARRY COSENZA ET AL: "Comparative model building of interleukin-7 using interleukin-4 as a template: A structural hypothesis that displays atypical surface chemistry in helix D important for receptor activation", PROTEIN SCIENCE, vol. 9, no. 5, 1 January 2000 (2000-01-01), pages 916-926, XP055539734

D1 discloses IL-7 variants for the reduction of the anti-IL-7 T-cell response. The substitution Gln22Asp (Q22D) is disclosed. The IL-7 variant may be fused to an Fc fragment or an immunoglobulin. The variant or fusion protein may be used for the treatment of cancer or HIV (Abstract, claims 1, 9 and 19).

D2 aims at the increase of the serum-half life of IL-7 by linking it to an Fc region (paragraph 43). IL-7 is modified in that position 116 is not glycosylated, or amino acids 96-114 are deleted (claims 1 and 7). Preferably, the Fc region is modified to increase the half-life by the substitution Asn297Gln or Phe296Ala in IgG1.

D3 discloses compositions comprising two IL-2 entities and one antibody binding CD4. Preferably, the IL-2 comprises mutations that reduce or abolish the interaction with the receptor. Furthermore, it is disclosed that the insertion of alanine between the antibody and IL2 increases the half-life of the fusion protein.

D4 discloses the substitution of the cysteine residues by serine in order to analyse the structural requirements of a functional IL-7. It is shown that the replacement of all six cysteines results in the inactivation of IL-7 whereas one cysteine pair allows binding of the IL-7 variant with reduced affinity to the IL-7 receptor (correspond to Cys2-Cys141, Cys34-Cys129 or Cys47-Cys92 of the application)(Abstract, Table III).

D5 is cited on page 2 of the application and is a review about immunocytokines.

D6 summarizes the known optimization options of the Fc-region of immunoglobulins. For example, the substitutions T250Q and M428L in IgG1 are disclosed to modify the half-life and N297A to silence effector functionality in IgG1 and S228P to stabilize IgG4 (Tables 2 and 3).

D7 discloses an alanine scanning approach to predict the structure of IL-7. The substitutions are K120A, L135A, K139A and W142A (numbering adapted to numbering of application). It is disclosed that W142 is important for receptor binding and activation and that the variant W142A acts as an IL-7R system antagonist (page 924, left-hand column, first paragraph).

2

Re Item IV

Lack of unity of invention

The application as filed is considered to lack unity of invention since its subject-matter relates not to one but rather to eight separate inventions not linked together by a common underlying inventive concept as required by Article 13.1 PCT.

The claims and the inventions to which the separate inventions relate may be grouped as indicated in the international search report.

Invention 1: claims: 2(completely); 1, 5-24(partially)

relate to a fusion protein comprising an IL-7 variant and a binding moiety, wherein the IL-7 variant has reduced affinity for the IL-7 receptor and an improved pharmacogenetic property said variant being characterized by the substitution W142H/F/Y; the corresponding nucleic acids, host cells, compositions and uses.

Invention 2: claims: 3(completely); 1, 5-24(partially)

relate to a fusion protein comprising an IL-7 variant and a binding moiety, wherein the IL-7 variant has reduced affinity for the IL-7 receptor and an improved pharmacogenetic property said variant being characterized by the substitution of four cysteine residues by serine residues; the corresponding nucleic acids, host cells, compositions and uses.

Invention 3: claims: 4(completely); 1, 5-24(partially)

relate to a fusion protein comprising an IL-7 variant and a binding moiety, wherein the IL-7 variant has reduced affinity for the IL-7 receptor and an improved pharmacogenetic property said variant being characterized by the substitution D74E/Q/N; the corresponding nucleic acids, host cells, compositions and uses.

Invention 4: claims: 1, 5-24(all partially)

relate to a fusion protein comprising an IL-7 variant and a binding moiety, wherein the IL-7 variant has reduced affinity for the IL-7 receptor and an improved pharmacogenetic property said variant being characterized by the substitution Q11E; the corresponding nucleic acids, host cells, compositions and uses.

Invention 5: claims: 1, 5-24(all partially)

relate to a fusion protein comprising an IL-7 variant and a binding moiety, wherein the IL-7 variant has reduced affinity for the IL-7 receptor and an improved pharmacogenetic property said variant being characterized by the substitution Y12F; the corresponding nucleic acids, host cells, compositions and uses.

Invention 6: claims: 1, 5-24(all partially)

relate to a fusion protein comprising an IL-7 variant and a binding moiety, wherein the IL-7 variant has reduced affinity for the IL-7 receptor and an improved pharmacogenetic property said variant being characterized by the substitution M17L; the corresponding nucleic acids, host cells, compositions and uses.

Invention 7: claims: 1, 5-24(all partially)

relate to a fusion protein comprising an IL-7 variant and a binding moiety, wherein the IL-7 variant has reduced affinity for the IL-7 receptor and an improved pharmacogenetic property said variant being characterized by the substitution Q22E; the corresponding nucleic acids, host cells, compositions and uses.

Invention 8: claims: 1, 5-24(all partially)

relate to a fusion protein comprising an IL-7 variant and a binding moiety, wherein the IL-7 variant has reduced affinity for the IL-7 receptor and an improved pharmacogenetic property said variant being characterized by the substitution K81R; the corresponding nucleic acids, host cells, compositions and uses.

- 2.1 The **common matter** linking together these inventions is the following: fusion protein comprising an IL-7 variant and a binding moiety, wherein the IL-7 variant has reduced affinity for the IL-7 receptor and an improved pharmacogenetic property.

This common matter does not comprise a single general inventive concept, based on same or corresponding special technical features. **D1** discloses an IL-7 variant with the substitution Gln22Asp (Q22D) which may be fused to an Fc fragment or an immunoglobulin and has the improved pharmacogenetic property of reduced immunogenicity (Abstract, claims 1 and 9). Although the reduced affinity for the IL-7 receptor is not shown, this is an implicit feature resulting from the substitution which is at the same position as one of the claimed substitutions (application: Gln22Glu = Q22E, D1: Gln22Asp = Q22D). Hence, the common matter is not novel over D1. Furthermore, the common matter is not novel over **D2**. Said document aims at the increase of the serum-half-life of IL-7 by linking it to an Fc region (paragraph 43), wherein IL-7 may be modified in that position 116 is not glycosylated or amino acids 96-114 are deleted (claims 1 and 7).

Independent from the objections in view of D1 and D2, the subject-matter of the present set of claims is not unitary. In particular, since fusion proteins comprising IL-7 and an Fc region are well-known in the art, the fusion proteins of inventions 1-8 do not share a significant structural element. A common functional feature is not sufficient to achieve unity.

- 2.2 Starting from the common concept, **invention 1** (for technical reasons also called "subinvention 1.1") comprises the additional feature of the substitution W142H/F/Y. The effect of said additional feature is that the affinity of the IL-7 fusion protein to the IL-7 receptor is decreased and the half-life measured as AUC is increased. Hence, invention 1 solves the problem of the provision of a fusion protein comprising IL-7 and a binding moiety which has decreased affinity for the IL-7 receptor and increased half-life.

Starting from the common concept, **invention 2** (for technical reasons also called "subinvention 1.2") comprises the additional feature of replacing four cysteine residues by serine residues. The effect of said additional feature is that the affinity of the IL-7 fusion protein to the IL-7 receptor is decreased and the half-life measured as AUC is increased. Hence, invention 1 solves the problem of the provision of a fusion protein comprising IL-7 and a binding moiety which has decreased affinity for the IL-7 receptor and increased half-life.

Starting from the common concept, **invention 3** comprises the additional feature of the substitution D74E/Q/N. The effect and the problem are as formulated for inventions 1 and 2.

Starting from the common concept, **invention 4** comprises the additional feature of the substitution Q11E. The effect and the problem are as formulated for inventions 1 and 2.

Starting from the common concept, **inventions 5 to 8** comprises the additional feature of the substitution Y12F, M17L, Q22E and K81R, respectively. The effect and the problem are as formulated for inventions 1 and 2.

- 2.3 In this context, it is observed that **inventions 4, 5 and 7** may even not share the common functional features. In particular, the effect is comprised in claim 1 as functional feature. However, the **examples do not provide any evidence** that said functional feature is achieved. Specifically, the variants Q11E, Y12F and Q22E do not clearly show a decreased affinity for the receptor and have not been tested for their half-life. If said effect of decreased affinity for the IL-7 receptor and increased half-life is not achieved, claims relating to said inventions do not share the common matter as identified above. In this case these inventions do even not share the functional feature with the other inventions and hence, solve a different problem and already for this reason the application lacks unity.
- 2.4 In summary, the features of inventions 1-8 which make a technical contribution over the common matter are different and not corresponding.
- 2.5 The present application claims priority from EP19306671. Said priority application was filed at the European patent office wherein **inventions 1 and 2 have been searched**. Hence, although inventions 1 and 2 are different inventions, a preliminary opinion is given for both inventions.

3 **Invention 1: fusion proteins with a binding moiety and an IL-7 variant having the substitution W142H/F/Y**

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3.1 **Novelty**

The subject-matter of all claims as far as relating to invention 1 is novel. None of the cited documents discloses a fusion protein comprising a binding moiety and an IL-7 variant having the substitution W142H/F/Y.

3.2 **Inventive step**

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of all claims as far as covered by invention 1 does not involve an inventive step in the sense of Article 33(3) PCT.

3.2.1 Firstly, the subject-matter of **claims 1, 2, 5-12, 21-24** is obvious.

Claims 1, 2 and 5 relate to a fusion protein comprising a binding moiety and an IL-7 variant with the substitution W142H/F/Y and having reduced affinity for the IL-7 receptor and improved pharmacokinetics, wherein the binding moiety is only functionally defined in that it "binds to a target specifically expressed on immune cells surface". In claims 6-12 and 21-24, the binding moiety is not clearly specified since only in preferred embodiments within one claims 6 and 7 reference is made to IgG1 or IgG4.

D1 may be taken as closest prior art document. The **difference** between the subject-matter claimed and D1 resides in the modification of IL-7, namely the substitution W142H/F/Y in the application versus the substitution Gln22Asp. An **effect** is shown for an IgG4 and IgG1 fusion protein comprising said IL-7 variant, namely strongly increased AUC values for W142H and decreased binding for all variants having the substitution W142H/F/Y. However, it is not credible that said effect is achieved for any other binding moiety. Hence, the objective **problem** is formulated as the provision of a further fusion protein comprising an IL-7 variant and a binding moiety.

The solution is obvious in view of **D7**. Said document discloses that W142 of IL-7 is important for receptor binding and activation and that the variant W142A acts as an IL-7R system antagonist (page 924, left-hand column, first paragraph). The skilled practitioner would combine the teaching of D1 with the teaching of D7 and arrive at the teaching of the afore-mentioned claims. Consequently, the subject-matter of all claims as far as relating to invention 1 is not inventive.

3.2.2 Secondly, the subject-matter of **claims 13-20** is obvious.

Said claims seem to relate to a dimer comprising two times an IL-7 - Fc fusion protein. The application shows that the fusion of the claimed IL-7 variants to IgG1m or IgG4m have a synergistic effect in that the binding of CD127 and pSTAT5 activation on human PBMCs are improved (example 3). However, this effect is not credible over the whole scope of the claims, i.e. for the numerous different constructs indicated in claims 13-16. In particular, the application seems to provide evidence only for IgG1m or IgG4m. Without any effect, the

inventive step objections of the previous paragraphs also apply for claims 13-20 since the fusion of a protein to Fc is already disclosed e.g. in D1, claim 9 and dimerization is an intrinsic feature of such Fc domains.

- 3.2.3 The subject-matter of all claims as far as directed to fusion proteins comprising IgG1 or IgG4 and an IL-7 variant covered by invention 1 is **novel and inventive**. Taking e.g. D1 or D2 as closest prior art document, the effect is the extended half-life of the fusion protein and improvement of the binding of CD127 and pSTAT5 activation on human PBMCs. Hence, the objective **problem** is the provision of fusion proteins comprising an IL-7 variant and an immunoglobulin wherein said fusion protein has an extended serum half-life and improvement of the binding of CD127 and pSTAT5 activation on human PBMCs. The solution is **inventive**. Although the skilled practitioner was motivated to produce further IL-7-immunoglobulin fusion proteins such as variants with amino acid substitutions, he did not have a reasonable expectation of success that the specific variants have the desired effect of increased serum half-life.

- 4 **Invention 2: fusion proteins with a binding moiety and an IL-7 variant having four cysteine residues replaced by serine residues**

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 4.1 **Novelty**

The subject-matter of all claims as far as relating to invention 2 is novel. None of the cited documents discloses a fusion protein comprising a binding moiety and an IL-7 variant having four cysteine residues replaced by serine residues.

- 4.2 **Inventive step**

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of all claims as far as covered by invention 2 does not involve an inventive step in the sense of Article 33(3) PCT.

- 4.2.1 Firstly, the subject-matter of claims **1, 3, 5-12, 21-24** is obvious.

Claims 1, 3 and 5 relate to a fusion protein comprising a binding moiety and an IL-7 variant having four cysteine residues replaced by serine residues and having reduced affinity for the IL-7 receptor and improved pharmacokinetics, wherein the binding moiety is only functionally defined in that it "binds to a target

specifically expressed on immune cells surface". In claims 6-12 and 21-24, the binding moiety is not clearly specified since only in preferred embodiments within one claim reference is made to IgG1 or IgG4.

D1 may be taken as closest prior art document. The **difference** between the subject-matter claimed and **D1** resides in the modification of IL-7, namely replacement of four cysteine residues in the application versus the substitution Gln22Asp. An **effect** is shown for an IgG4 and IgG1 fusion protein comprising said IL-7 variant. However, it is not credible that said effect is achieved for any other binding moiety. Hence, the objective **problem** is formulated as the provision of a further fusion protein comprising an IL-7 variant and a binding moiety.

The solution is obvious in view of **D4**. Said document discloses the substitution of the cysteine residues by serine in order to analyse the structural requirements for a functional IL-7. It is shown that the replacement of all six cysteines results in the inactivation of IL-7 whereas maintenance of one cysteine pair allows binding of the IL-7 variant to the IL-7 receptor with reduced affinity (substitutions correspond to Cys2-Cys141, Cys34-Cys129 or Cys47-Cys92 of the application)(Abstract, Table III). The skilled practitioner would combine the teaching of **D1** with the teaching of **D4** and arrive at the teaching of the afore-mentioned claims. Consequently, the subject-matter of all claims as far as relating to invention 1 is not inventive.

- 4.2.2 Secondly, the subject-matter of **claims 13-20** is obvious for the same reasons as indicated for invention 1.

Said claims seem to relate to a dimer comprising two times an IL-7 - Fc fusion protein. The application shows that the fusion of the claimed IL-7 variants to IgG1m or IgG4m have a synergistic effect in that the binding on CD127 and pSTAT5 activation on human PBMCs are improved (example 3). However, this effect is not credible over the whole scope of the claims, i.e. for the numerous different constructs indicated in claims 13-16. In particular, the application seems to provide evidence only for IgG1m or IgG4m. Without any effect, the inventive step objections of the previous paragraphs also apply for claims 13-20 since the fusion of a protein to Fc is already disclosed e.g. in **D1**, claim 9 and dimerization is an intrinsic feature of such Fc domains.

- 4.2.3 The subject-matter of all claims as far as directed to fusion proteins comprising IgG1 or IgG4 and an IL-7 variant covered by invention 2 is **novel and inventive** (same reasoning as for invention 1). Taking e.g. **D1** or **D2** as closest prior art document, the effect is the extended half-life of the fusion protein and

improvement of the binding of CD127 and pSTAT5 activation on human PBMCs. Hence, the objective **problem** is the provision of fusion proteins comprising an IL-7 variant and an immunoglobulin wherein said fusion protein has an extended serum half-life and improvement of the binding of CD127 and pSTAT5 activation on human PBMCs. The solution is **inventive**. Although the skilled practitioner was motivated to produce further IL-7-immunoglobulin fusion proteins such as variants with cysteine-serine substitutions, he did not have a reasonable expectation of success that the specific variants have the desired effect of increased serum half-life.

5 **Re Item VIII**

Certain observations on the international application (apply for all inventions)

- 5.1 The term "binding moiety" and "improves pharmacokinetics" are broader than justified by the description and not enabled over the whole scope of the claim (Articles 5 and 6 PCT).
- 5.2 **Claims 13-20** are unclear. In particular, it seems that the "monomer" is the "bifunctional molecule" of the previous claims and that the Fc chain is the "binding moiety" of the previous claims. Furthermore, said claims lack conciseness in that all possible positions of the Fc region with or without variable domain are listed.
- 5.3 **Claims 18-20** are unclear since the function of the sequences identified by SEQ ID NO is not specified. The objection may be overcome by indicating the protein to which the antibody binds.
- 5.4 Finally, the optional and preferred embodiments in several claims make the claims unclear (see e.g. claims 6-8, 10-12).