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17 August 2022

By E-mail Only

Dear Yvette

Singapore (SG) Patent Application No: 11201904012T
National Phase of International (WO) Patent Application No: PCT/EP2017/083051
Applicant(s): SINGAPORE HEALTH SERVICES PTE LTD; NATIONAL UNIVERSITY OF SINGAPORE
Title: IL-11 ANTIBODIES
Your Ref: AY/YF/as/2019.P01532
Mewburn Ref: 007480676

Please prepare a Request for an Examination Review Report based on the enclosed amended claims and the following comments.

If possible, we wish to file the Request in time to meet the **22 August 2022** deadline. However, if necessary, please make use of a further month's extension of time (*i.e.* until 22 September 2022).

1. Introductory comment

For your information, it is important to our client to retain claim coverage for antibodies/fragments having the following combination of CDRs, which comprise a single amino acid difference in LC-CDR3 relative to the CDRs of YU100-G08 (bold and underlined):

VL comprising:
- LC-CDR1: SSDVGGYNY
- LC-CDR2: DVN
- LC-CDR3: **A**SYAGRYTWM

VH comprising:
- HC-CDR1: GFTFSSYG
- HC-CDR2: ISYDGSNK
- HC-CDR3: AKIGATDPLDY

2. Amendments

Claim 1 is amended to specify that the antibody/fragment inhibits IL-11-mediated signalling. Support for the amendment is found *e.g.* at page 46, line 34 of PCT/EP2017/083051 as filed.

Claim 9 is amended to specify that the disease/disorder characterised by fibrosis selected from: pulmonary fibrosis, atrial fibrillation, ventricular fibrillation, hypertrophic cardiomyopathy (HCM),

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dilated cardiomyopathy (DCM), non-alcoholic steatohepatitis (NASH), cirrhosis, chronic kidney disease, scleroderma, systemic sclerosis, keloid, cystic fibrosis, Chron's disease, post-surgical fibrosis, retinal fibrosis and retinal fibrosis associated with wet age-related macular degeneration (AMD). Support for the amendment is found *e.g.* at page 60, lines 26 to 30.

Claim 11 is amended to correct an obvious typographical error, with no change in the subject-matter claimed.

Previous claim 12 is deleted.

Claim 13 (previous claim 14) is currently amended to specify that the cancer is selected from: an epithelial cell cancer, breast cancer, gastrointestinal cancer, esophageal cancer, stomach cancer, pancreatic cancer, liver cancer, hepatocellular cancer, gallbladder cancer, colorectal cancer, colonic cancer, anal cancer, gastrointestinal carcinoid tumor, lung cancer, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC) and lung adenocarcinoma. Support for the amendment is found *e.g.* at page 61, lines 5 to 10 and 31 to 35.

Previous claims 15 and 16 are deleted.

The remaining claims and their dependencies are renumbered accordingly.

3. Clarity (Section 25(5)(b) of the *Patents Act*)

The Examiner objects that previous claim 9 lacks clarity for failing to specify the particular diseases/disorders characterised by fibrosis to be treated/prevented in accordance with the claimed medical use.

Claim 9 is currently amended to recite the diseases/disorders characterised by fibrosis specified in previous claim 12. Accordingly, the Examiner's objection is addressed.

The Examiner similarly indicates that the same consideration applies to claim 13, with respect to diseases/disorders characterised by inflammation. However, we note that claim 12 (previous claim 13) already specifies the diseases/disorders characterised by inflammation to be to be treated/prevented, and so we understand that further amendment is not necessary.

The Examiner also identifies a typographical error in claim 11, which is rectified in the present claims.

4. Support (Section 25(5)(c) of the *Patents Act*)

4.1 Claim 1 permitting an amino acid substitution in LC-CDR3

The Examiner alleges that claim 1 lacks support as it permits substitution of an amino acid residue of LC-CDR3. The Examiner considers that it would amount to an undue burden for the skilled person to test variant antibodies satisfying the structural terms of claim 1, to determine which antibodies retain IL-11 binding activity.

As noted under section 1 above, our client wishes to retain claims encompassing the YU100-G08 variant comprising 'A' at position 1 of LC-CDR3.

The following paragraphs provide our comments in relation to support for claim 1 as currently amended.

Claim 1 relates to an IL-11-binding antibody/antigen-binding fragment defined in structural terms by reference to the heavy and light chain CDRs of anti-IL-11 antibody clone YU100-G08.

YU100-G08 is demonstrated in the application to bind to IL-11 and inhibit IL-11-mediated profibrotic signalling – see *e.g.* Example 16.2 and Figures 56A and 56B.

While claim 1 permits a single amino acid substitution in LC-CDR3 relative to the CDRs of YU100-G08, all other CDRs are required to be identical to those of YU100-G08. Thus, claim 1 relates to antibody/fragments having the CDRs of YU100-G08, or comprising a single amino acid substitution in LC-CDR3, and therefore having at least 98% amino acid sequence identity to the CDRs of YU100-G08 (*i.e.* 48/49 CDR amino acid residues). The claimed antibodies/fragments are defined in structural terms based extremely closely on YU100-G08.

Present claim 1 moreover imparts limitations on the functional properties of the claimed antibodies/fragments, requiring that they bind to IL-11 and inhibit IL-11-mediated signalling.

The skilled person is able to obtain antibodies as defined in claim 1 with certainty and without undue burden. More specifically, the skilled person is readily able – in view of the specification and their common general knowledge – to produce antibodies having the structural features as defined in claim 1, and evaluate such antibodies for their ability to bind to IL-11 and inhibit IL-11-mediated signalling.

The person skilled in the art is able to produce antibodies and fragments comprising VH and VL regions comprising the specified combinations of heavy and light chain CDRs. They are also readily able to obtain antibodies/fragments comprising an amino acid substitution in LC-CDR3, as a matter of routine using well-known techniques, such as *e.g.* site-directed mutagenesis.

The skilled person is also readily able in view of the specification and their common general knowledge to determine which antibodies having the structural features of claim 1 possess the requisite functional properties, *i.e.* those that bind to IL-11 and inhibit IL-11-mediated signalling.

The specification explains that the antibodies described therein were evaluated for their ability to bind to IL-11 by analysing their ability to bind to HEK cells expressing IL-11, as determined by flow cytometry (see Example 8), and by ELISA (see Example 6.4, 16.1), and describes further suitable techniques for investigating binding of antibodies/fragments to a given target antigen at page 47, line 40 to page 48, line 5.

The specification moreover explains that the antibodies described therein were evaluated for their ability to inhibit IL-11-mediated signalling, in assays analysing their ability to inhibit TGFβ1-induced activation of fibroblasts to activated, αSMA-positive myofibroblasts (see Example 6.1, 16.2), and describes further techniques for investigating the ability of antibodies/fragments to inhibit IL-11-mediated signalling *e.g.* at page 51, lines 1 to 3.

The skilled person is therefore able in view of the specification and their common general knowledge to obtain antibodies and antigen-binding fragments having the structural features and functional properties specified in claim 1, with certainty and without undue burden.

Post-filing date publication WO 2019/238882 A1 (enclosed) moreover confirms that antibodies comprising a single substitution in LC-CDR3 according to claim 1 retain the ability to bind to IL-11 and inhibit IL-11-mediated signalling. Antibodies 02A, 02G, 02I, 02L, 02Q, 02S, 02T and 02V disclosed in WO 2019/238882 A1 each comprise VH and VL regions according to claim 1, comprising a single amino acid difference in LC-CDR3 relative to CSYAGRYTWM. Example 19.1 and Figure 35 of WO 2019/238882 A1 demonstrate that each of these antibodies binds to IL-11, and Example 20 and Figure 38 discloses their ability to inhibit IL-11-mediated signalling.

***We have alternatively considered amending claim 1 as follows:

1. An antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, wherein the antibody or antigen binding fragment comprises:
(i) a light chain variable region sequence comprising the following CDRs:
LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: CSYAGRYTWM (SEQ ID NO:336), or a variant comprising ~~1~~an amino acid substitution at position one of ~~in the sequence~~ CSYAGRYTWM (SEQ ID NO:336), and
(ii) a heavy chain variable region sequence comprising the following CDRs:
HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187);
and wherein the antibody or antigen binding fragment inhibits IL-11-mediated signalling.

We note that Figure 48C at page 130 of the drawings identifies position 1 of LC-CDR3 as a position at which variance is contemplated, and also that LC-CDR3 = **A**SYAGRYTWM (see section 1 above) conforms to the consensus sequence of SEQ ID NO:404 wherein X_{159} = A, X_{160} = R, X_{161} = Y, X_{162} = T and X_{163} = M.

While we think this amendment might be helpful to address the objection under Section 25(5)(c), we are mindful that it might be considered by the Examiner to present an issue under Section 84(3) of the *Patents Act*.

Please advise whether you recommend to amend claim 1 as shown above, in view of your experience of IPOS' practice in relation to evaluation of subject-matter disclosed in the application as filed.***

4.2 Use of the claimed antibody in the treatment/prevention of diseases characterised by inflammation

The Examiner alleges that claim 13 lacks support as it they consider that there is inadequate evidence that the claimed antibody/fragment will be (or is likely to be) effective to treat/prevent inflammation. The Examiner points to a section of the description referring to studies that had suggested that IL-11 signalling was anti-inflammatory, playing a protecting role in inflammation.

Please argue against the objection, as follows.

Page 36, lines 25 to 28 of the description referred to by the Examiner cites Trepicchio and Dorner Expert Opin Investig Drugs (1998) 7: 1501–1504 and Zhu *et al.*, PLoS ONE (2015) 10, e0126296.

Trepicchio and Dorner Expert Opin Investig Drugs (1998) 7: 1501–1504 is an opinion article referring to the results of studies in which recombinant human IL-11 was investigated in rodent models of inflammatory disease (see *e.g.* page 1502, right column, second paragraph and paragraph spanning pages 1502-1503). Similarly, Zhu *et al.*, PLoS ONE (2015) 10, e0126296 investigates the effects of recombinant human IL-11 in a mouse model of liver ischemia/reperfusion injury (see *e.g.* page 3, first paragraph).

The specification also explains that several studies have reported pro-inflammatory effects for IL-11. Page 62, lines 10 to 21 summarise reports implicating IL-11-mediated signalling in various diseases/disorders characterised by inflammation.

The specification moreover explains at page 80, lines 11 to 19 that the conflicting reports in the prior art as to the role of IL-11 in fibroinflammatory processes might have arisen as a consequence of human IL-11 being employed in rodent models of disease (with reference to Trepicchio and Dorner, 1998), and moreover demonstrates that human IL-11 does not cause activation of mouse fibroblasts.

The experimental examples go on to unequivocally demonstrate that IL-11-mediated signalling is a pro-inflammatory and pro-fibrotic, for example causing upregulation of expression of the pro-inflammatory cytokine IL-6 – see *e.g.* Figures 6C, 7D.

Thus, the application supports that anti-IL-11 antibodies/fragments that inhibit IL-11-mediated signalling are indeed useful for the treatment/prevention of diseases/disorders characterised by inflammation.

Post-filing date publication WO 2019/238882 A1 moreover provides confirmatory evidence that anti-IL-11 antibody antagonists of IL-11-mediated signalling attenuate inflammation *in vivo*. IN particular, Example 14.3 and Figure 43 confirm that blocking IL-11-mediated signalling using a neutralising anti-IL-11 antibody inhibits liver inflammation in a mouse model of non-alcoholic steatohepatitis (NASH), as determined by analysis of the expression of the inflammation markers TNFα, CCL2 and CCL5.

4.3 Use of the claimed antibody in the treatment/prevention of cancers

Finally, the Examiner alleges that while it is considered plausible from the prior art that anti-IL-11 antibodies are useful in the treating various types of cancer, they do not consider that they will be useful in all types of cancer.

Present claim 13 is currently amended to specify the treatment/prevention of cancers that would reasonably derive benefit from intervention to antagonise IL-11-mediated signalling, in view of the cancers in which IL-11 is disclosed to be pathologically-implicated in the prior art.

The specification at page 61, lines 5 to 20 explains that IL-11 signalling is implicated in cancers of the gastrointestinal tract, including gastrointestinal tumors, gastric (stomach) and colorectal (*e.g.* colonic) cancers, and also in liver (*e.g.* hepatocellular), breast and lung cancers (*e.g.* lung adenocarcinoma, a kind of NSCLC). Putoczki and Ernst, Immunotherapy (2015) 7(4):441-53 (enclosed) is a review article relating to IL-11-mediated signalling in cancer, and further explains that elevated IL-11 signalling is associated with cancers of epithelial origin (see page 445, paragraph spanning left and right columns) and in breast, colorectal, liver, lung, pancreatic and stomach cancers (see Table 3 on page 446).

Accordingly, the Examiner's objection is addressed.

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Please let me know if you have any questions or comments. Otherwise, we look forward to receiving your comments on possible further amendment to claim 1 (as detailed in section 4.1 above) at your earliest convenience, with a view to preparing and filing the Request for an Examination Review Report in time to meet the **22 August 2022** deadline. Thank you.

Yours sincerely,

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Enc. Amended claims (showing changes)
WO 2019/238882 A1
Trepicchio and Dorner Expert Opin Investig Drugs (1998) 7: 1501–1504
Zhu *et al.*, PLoS ONE (2015) 10, e0126296
Putoczki and Ernst, Immunotherapy (2015) 7(4):441-53