

European Patent Office
D-80298 Munich
Germany

Our ref GJT/R79952OP

12 January 2024

Opponent 1: Notice of Appeal

Re: European Patent No. 3 539 548 (Application No. 19168383.8)
The University of Tokyo
Opponent O1: Société des Produits Nestlé S.A.

On behalf of Opponent 1, Société des Produits Nestlé S.A., of Avenue Nestlé 55, 1800 Vevey, Switzerland, we hereby file a Notice of Appeal under the provisions of Articles 106 to 108 EPC against the decision of the Opposition Division dated 13 November 2023.

We request that the decision to reject the oppositions be set aside and that the European patent be revoked.

The appeal fee is being paid from our deposit account as indicated in the accompanying fee sheet. You are authorised to remedy any deficiency in the fee by debiting our deposit account no. 2805.0051 (Elkington and Fife LLP).

Our Grounds of Appeal will follow within the period provided by Article 108 EPC.

Yours faithfully
Elkington and Fife LLP

[Signed Electronically]

Glyn Truscott

European Patent Office
D-80298 Munich
Germany

Our ref HCR/ALB/R79952OP

12 March 2024

ONLINE FILING

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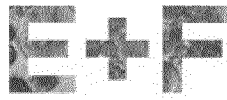
We are writing further to our letter of 12 January 2024, to enclose the opponent/appellant's grounds of appeal.

Yours faithfully

Elkington and Fife LLP

[Signed Electronically]

Henrietta Rooney



ELKINGTON + FIFE

European patent no. EP3539548

(application no. 19168383.8)

The University of Tokyo

Opponent 1: Société des Produits Nestlé S.A.

GROUND OFS OF APPEAL

1. Requests

(01) We request that the Opposition Division's decision of 13 November 2023 to maintain the patent as granted be set aside and that the patent be revoked.

(02) Oral proceedings are requested in the event that the Board is minded not to revoke the patent.

2. Background

(03) The application that led to the patent is a divisional application from EP16188203.0 (now granted as EP 3 178 483), which is referred to herein as the "parent" application. The parent application is itself a divisional application from EP11728077.6 (granted as EP 2 575 835), which is referred to herein as the "grandparent" application.

(04) The grandparent case was opposed by multiple parties including the current Opponent 1, Société des Produits Nestlé S.A.

(05) When the current opposition was filed, the decision of the Opposition Division on the grandparent case was under appeal. Those appeal proceedings concluded with the Board of Appeal (3.3.08) issuing its preliminary opinion (D67) that the grandparent patent as granted and all Auxiliary Requests were invalid.

(06) In reply to that opinion from the Board, the Patentee disapproved the text for grant and thereby self revoked the grandparent patent. The grandparent patent is therefore revoked. This was duly noted by the current Opposition Division.

(07) The claims of the currently opposed patent encompass features that the Board of Appeal in the grandparent case considered not to comply with the EPC.

(08) Notably, the Board of Appeal disagreed with the Opposition Division's decision at first instance on the grandparent case to maintain the grandparent patent as amended, and instead was minded to revoke the patent.

(09) Despite considering the Board of Appeal's opinion (D67), the Opposition Division in the current case followed the decision of the Opposition Division on the grandparent case, rather than following the later preliminary opinion of the Board of Appeal, which found fault with the reasoning of the Opposition Division in the grandparent case.

(10) The Opposition Division's decision that the patent can be maintained as granted is therefore in conflict with the Board of Appeal's opinion on the same issues in the parent case. The Board of Appeal's opinion (D67) principally addresses the added matter and insufficiency in the claimed subject-matter in the grandparent patent.

(11) It is particularly noteworthy that the Board of Appeal considered that the definition of the active ingredient (bacteria of the genus *Clostridium*, comprising spore forming bacteria of *Clostridium* clusters IV and XIVa in combination) in the grandparent patent was not sufficiently described by the technical disclosure of the patent.

(12) The definition of the active ingredient is **significantly broader** (bacteria of the genus *Clostridium*) in the claims of the current patent than in the grandparent patent. The claims of the present patent therefore encompass subject-matter that the Board of Appeal considered not to be enabled, and for this reason alone the OD's decision on this point cannot be correct.

(13) Moreover the extension of the subject-matter of the present claims beyond that which the BoA already considered to lack enablement, presents an even higher undue burden on for the skilled person. The claimed definition of the active ingredient cannot, therefore, be enabled across its scope.

(14) However, the Opposition Division in the present case chose to diverge from the opinion of the Board in the grandparent case and regarded the Preliminary Opinion of the Board of Appeal (D67) to be "*very general*" and that the Board's assessment of sufficiency "*cannot be considered as convincing*". See section 8.6 of the OD's decision in the current case. For the reasons set out below, this decision was incorrect, and the OD should have followed the well-thought out, complete and convincing preliminary opinion of Board 3.3.08 on the grandparent case.

3. Summary

(15) The Opposition Division (OD) decided to maintain the patent as granted. However, this decision was wrong because these claims do not meet the requirements of the EPC. We set out below why the OD's decision to maintain the patent as granted is wrong and should be set aside.

(16) The patent does not provide a clinically-relevant advance over the art. The medical use claims are therefore invalid.

(17) The patent relates generally to the use of *Clostridium* bacteria to induce accumulation of regulatory T cells. The claims relate to a pharmaceutical composition for use in a method for suppressing the immunity of a subject to prevent or treat an autoimmune disease or an allergic disease by inducing proliferation or accumulation of transcription factor Foxp3-positive regulatory

T cells. The pharmaceutical composition comprises, as an active ingredient, bacteria belonging to the genus *Clostridium* that induce said proliferation or accumulation of transcription factor Foxp3-positive regulatory T cells. Inflammatory bowel disease (IBD) is claimed as an example of an autoimmune disease. There is no example in the patent that falls within the claim scope.

(18) There is a very significant failing in the patent because there is **no evidence in the patent** that the claimed composition comprising bacteria belonging to the genus *Clostridium* is able to provide the claimed therapeutic effect: treatment or prevention of autoimmune disease or allergic disease. The patent therefore **fails to disclose the suitability of the claimed composition for the claimed therapeutic use**.

(19) The patent is based on data allegedly showing that a particular combination of specific *Clostridium* bacteria has an effect on Foxp3-positive regulatory T cells in the colon. The autoimmune data in the patent therefore relate specifically and only to the local interaction of cells in the colon, so any alleged effect is **strictly limited to the colon**. These data are also limited to a **specific combination of *Clostridium* bacteria** from a model system, and do not credibly show that the observed affect will be provided by any and all bacteria of the genus *Clostridium*.

(20) There is no evidence in the patent that substantially any and all bacteria from the genus *Clostridium* are able to prevent or treat diseases across the claim scope, by the claimed mechanism. The extremely broad claim scope is not credible in view of the very limited data in the patent.

(21) The patent is not entitled to either priority date, meaning that multiple disclosures made by the inventors during the priority year invalidate the claims. The opposition division erred in deciding on the effective date of the claimed subject matter, and therefore erred in its decisions on novelty and inventive step as explained herein.

(22) In particular, the claims lack novelty over: the inventors' own disclosures during the priority year; the known use of donor faeces to treat gastrointestinal diseases such as inflammatory bowel disease (IBD) in patients, wherein the donor faeces will inevitably contain bacteria belonging to the genus *Clostridium*; the disclosure of bacteria of *Clostridium* Cluster XIVa to treat mouse models of IBD by inducing Foxp3+ Tregs; and disclosures of bacterial combinations comprising *Clostridium* for the treatment of inflammatory bowel disease (IBD) in human patients.

(23) The granted claims unallowably add matter over the application as filed and the parent/grandparent application as filed. These claim features unallowably improved the Patentee's position compared to the application as filed, contrary to G1/93. The OD erred in deciding that the claimed subject matter had basis in the application as filed.

4. Documents

(24) D1 to D74 and D77 were admitted into the proceedings before the OD.

(25) No decision was made on the admissibility of the other documents – D75, D76 and D78 to D80, which were all late-filed by the Patentee. If the Patentee intends to rely on any of these documents in its reply to this appeal, then we request that these documents are not admitted into the proceedings for the first time on appeal.

5. Interpretation of the term “genus” Clostridium

(26) In section 6 of its Decision, the OD decided that the term “genus” Clostridium must be interpreted taxonomically, i.e. referring to Clostridium spp. This is, in essence, a narrow definition. The OD erred in stating, in section 6.1.2 that this definition “respects implicitly the approaches suggested by the parties”, when there has been disagreement on this point throughout the proceedings.

(27) The Patentee presented a new interpretation at the hearing before the OD in the current proceedings, that the term “genus Clostridium” should be interpreted “phenetically” which is so broad as to be almost meaningless: endospore-forming anaerobes. We cannot recall that this interpretation was previously presented in the extensive proceedings on the grandparent patent or in the other parallel cases in this family. The Patentee’s new “phenetic” interpretation is in contrast to its position in the opposition proceedings in respect of the grandparent patent, where the Patentee maintained a “phylogenetic” definition that that the person skilled in the art would not draw a distinction between the terms “genus Clostridium” and “Clostridia”, such that bacteria that are not “Clostridium spp.” are still of the “genus Clostridium”.

(28) What is critical to errors in the OD’s decision, is that the OD has not consistently applied its taxonomic definition throughout the decision. As discussed below in respect of entitlement to priority, the definition of the term “genus Clostridium” was different in P1 and P2 as compared to the interpretation taken by the OD. The OD also refers in section 8.3.7 of the decision to the skilled person being able to provide bacteria of the genus Clostridium by using 16S rRNA analysis to identify such bacteria – despite accepting that this method will also identify bacteria of the suprageneric cluster IV which includes at least *F. prausnitzii* and having rejected the use of 16S rRNA analysis as defining whether a bacteria is of the genus Clostridium or not. This approach cannot be correct. Consistent interpretation of the meaning of this term is essential.

6. Added matter – Article 123(2) EPC and Article 76(1) EPC

(29) The claims as granted contain several features that unallowably add matter, both individually and when taken together, over the content of the application as filed (and, in turn, over the content of the parent application as filed). The OD erred in its assessment of added matter, which must be **assessed strictly** to protect the certainty of third parties and to prevent the applicant from improving its position after filing.

(30) The Patentee has greatly improved its position by writing claims that are **not directly and unambiguously disclosed** in the application as filed. In particular, the cumulative effect of multiple issues of added matter clearly improved the Patentee’s position by changing the claims to recite subject matter that was not described as part of the original disclosure. The claims

therefore give the Patentee a significant monopoly that was not described when the application was filed.

(31) Claim 2 as granted unallowably adds matter over the application as filed and the parent application as filed, contrary to Article 123(2) EPC and Article 76(1) EPC. This claim was amended during prosecution to recite that the autoimmune disease is “chronic inflammatory bowel disease”. This disease is only mentioned once in the application (and parent application) as filed, as part of a list at page 33 lines 22 to 24. This represents a selection from a list.

(32) The selection from a list in claim 2 is problematic because claim 1 already required the selection of “Foxp3-positive” cells, which are not the only regulatory T cells described in the application as filed. Page 28 lines 7 to 11 of the application as filed describes that the regulatory T cells that are induced can be Foxp3-positive T cells or IL-10 producing regulatory T cells. Therefore, selecting Foxp3-positive T cells is a first selection. The second selection, in claim 2, is of “chronic inflammatory bowel disease”. These multiple selections are not directly and unambiguously described in the application as filed, or the parent application as filed, and claim 2 therefore does not comply with Article 123(2) EPC or Article 76(1) EPC.

(33) The dosages in claim 5 and claim 6 represent further unallowable selections from the options presented at page 48 lines 2 to 5 of the application as filed. The isolation of these options provides further combinations of features that are not described in the application as filed or the parent application as filed.

(34) The formulations of claim 7 and claim 8 are yet further unallowable selections from lists that require additional selections when dependent upon claim 1 or claim 2, and in turn when dependent upon claim 5 or claim 6 – or, for claim 8, when additionally dependent upon claim 7.

(35) The coating agent of claim 7 is described in a long list of around 30 formulation options starting at page 38 line 21 and ending at page 39 line 7 of the parent application as filed. The selection of a coating agent is a clear selection from a very long list.

(36) The oral capsule of claim 8 is also described in a very long list of possible oral or parenteral pharmaceutical formulations starting at page 38 line 10 and ending at page 38 line 20 of the parent application as filed. The selection first of the oral option, then of capsule from this long list, is itself a double selection, and in turn creates yet further undisclosed combinations when dependent upon claims 1, 2, 5, 6, or 7.

(37) Therefore, claims 2, 5, 6, 7 and 8 lack basis in the application as filed and the parent application as filed.

(38) The objection applies under Article 76(1) EPC and 123(2) EPC for claim 2 which was amended during prosecution.

(39) Claims 5, 6, 7 and 8 were present in the claims as filed with this divisional application. Therefore, when dependent upon claim 1 (and each other) the objection applies under Article

76(1) EPC because the parent application as filed does not disclose the subject matter of these claims. When claims 5, 6, 7 and 8 are dependent upon claim 2, the objection is under Article 123(2) EPC because of the change in subject-matter caused by the amendment to claim 2 during prosecution.

6.1 The combination of amendments gives rise to new technical content

(40) It is important to consider the effect of the combination of the amendments relative to the application as filed. There is no single passage in the application as filed that discloses all of the features of the claimed subject matter in combination. The applicant has cherry-picked from throughout the description and drafted a claim that gives rise to new technical information that was not made available by the application as filed. Indeed, the **claimed subject matter would be deemed novel over the disclosure of the application as filed.**

(41) The Patentee has chosen to single out and combine certain features from the description. The application as filed was not directed to this specific combination of features, nor is this combination clearly and unambiguously derivable from the application as filed by the person skilled in the art. By making this new combination of features in the claim, the Patentee has given itself an unwarranted advantage and has presented the skilled person with new technical information that could not be derived directly and unambiguously from the application as filed, contrary to the principles established in G2/10. When considering these significant changes between the application as filed and what is claimed, it must be remembered the **strict test** set by the Boards of Appeal, that the slightest doubt (e.g. T383/88) as to the derivability of an amendment from the application as filed rules out the amendment.

(42) The Opposition Division's decision was based on the incorrect approach that the claims as granted find basis in the application as filed because the features are disclosed individually and therefore there are no new combinations of features.

(43) Specifically, the OD agreed with the Opponents that there have been multiple selections when creating the presently claimed subject matter, but section 7.2 of its decision asserts that the claimed combinations are disclosed because each feature is disclosed in an individualised manner and that the original wording of the claim is a type of "scaffold" to which additional features can be added.

(44) This analysis is incorrect.

(45) In section 36 of D67, the Board of Appeal specifically rejects the approach that the OD took, stating that the application as filed must not be considered as a reservoir of terms and that the claimed features are a combination of features combined to "artificially create a particular embodiment" that is not part of the technical disclosure of the application as filed:

36. At present, the board is not persuaded by the patent proprietor's counter-argument (see reply, paragraphs 65i and 66). It is well established in the case law of the boards of appeal that the content of an application must not be considered to be a reservoir from which features pertaining to separate embodiments of the application can be combined in order to artificially

(46) The OD's view that the claimed combinations of features do not add matter is therefore incorrect.

6.2 Each therapeutic application is a separate disclosure

(47) In section 7.4 of its decision, the OD commented that specifying the disease to be prevented does not add a new independent feature to the claims over and above the disclosure of the use of the claimed bacteria in therapy in general.

(48) This cannot be correct.

(49) Defining a particular disease to be treated can form a novel feature as compared to the general disclosure of a composition for use in therapy in general (see Art 54(4) and (5) EPC). Therefore, each individual therapeutic application is a separate, independent disclosure. Direct and unambiguous basis is required to combine any individual disclosure with other features, and this is lacking for the claimed combinations of features.

6.3 The Opposition Division's reasoning is inconsistent

(50) The OD's reasoning that there are no new combinations in the granted claims, is based in part on the view that the definition of the type of T regs is not an "independent" feature – i.e. that this feature of inducing FoxP3+ Tregs in particular is inexorably linked to the other features of the claim. This implies that it is inherent that using clostridia in general in a medical use will inevitably result in inducing proliferation or accumulation of transcription factor Foxp3-positive regulatory T cells. Despite taking this view on added matter, the OD did not consistently apply this same reasoning in assessment of novelty or inventive step.

(51) The OD has also commented in section 7.9.1 that the claimed combinations do not provide the skilled person with any new technical teaching beyond the content of the application as filed – a view is consistent with the point immediately above that the type of T regs is not an "independent feature", but which is inconsistent with later reasoning that the induction of FoxP3+ Tregs was not obvious over the disclosure of the prior art. If this feature is not a new technical teaching, it cannot be used to justify or support an inventive step of the claimed subject matter.

6.4 Summary of Added Matter

(52) These significant, numerous added matter issues result in the Patentee having unallowably improved its position compared to the parent application as filed (G1/93). It is not

allowable to treat the application as a reservoir of terms to be picked and mixed at will. The Patentee does not have the benefit of any doubt, because the slightest doubt rules out an amendment under Article 76(1) EPC and/or 123(2) EPC.

7. Sufficiency of Disclosure

(53) The claimed invention requires that any autoimmune disease or any allergic disease can be prevented or treated, using any bacteria, alone or in combination, from the genus *Clostridium* to induce proliferation or accumulation of transcription factor Foxp3-positive regulatory T cells.

(54) The claims therefore rest on the premise that proliferation or accumulation of transcription factor Foxp3-positive regulatory T cells will treat or prevent substantially **any** allergic or autoimmune disease; and that a clinically significant level of proliferation or accumulation of transcription factor Foxp3-positive regulatory T cells can be achieved by a composition comprising any amount of any bacteria from the genus *Clostridium*.

(55) The **patent must make it plausible** that the claimed medical uses will be achieved (e.g. T609/02). The patent plainly **fails** to meet this standard. The claim breadth is **not at all commensurate with the technical disclosure** (e.g. T189/09). This excessive claim breadth results in an **undue burden** on the skilled person to determine whether a given disease can be treated, which amounts to a research project.

(56) There is simply no evidence to suggest that the claimed treatment of an extremely wide-ranging variety of diseases can be achieved. Indeed, the data in D20 and D23 show that many bacteria from the genus *Clostridium* do **not** provide the alleged mechanistic effect of Tregs, let alone a therapeutic effect. For example, a combination of several *Clostridium* strains (i.e. significantly more than is required by the claims, which encompass a single strain) was **unable** to induce the accumulation of FoxP3 Tregs. This confirms that the extrapolation, from the limited data in the patent to the claim scope, is implausible.

(57) As noted by the OD in sections 8.2 and 8.2.1 of the decision, the data on file provided more evidence of non-working examples than of working examples falling within the scope of the claims. In fact, the OD referred directly to strains 4 and 7 of D23 as likely to be of the taxonomic genus *Clostridium*. These bacteria are shown in D23 not to induce the proliferation of Foxp3+ T regs, yet the OD refers to these strains in support of their decision on enablement.

(58) A particular weakness in the reasoning provided by the OD is linked to the interpretation of the meaning of the term “genus” *Clostridium*.

(59) As shown in the minutes, the OD did not decide on the taxonomic definition of the term until after deciding on sufficiency. Discussion of the definition of the term arises at point 58 of the minutes at the end of day 1, after a decision on sufficiency of the claims and entitlement to priority had already been made. However, the identity of the strains of “*Clostridia*” used in the patent is never given – the taxonomic names are missing. This is not reflected in the written decision, however, which presents the arguments in a different order to the order in which they were

discussed at the hearing. This is clear from section 8.3.7 of the decision, which refers to using phylogenetic analysis of 16S rRNA to identify bacteria of the genus *Clostridium* when discussing enablement.

7.1 There is no plausible link between the claimed compositions and the treatment of the claimed diseases

(60) Not only is there no technical justification for the breadth of the claims that were maintained by the OD, the patent also fails to provide a plausible link between the compositions of and the mechanism underlying the claimed method of treatment for allergic and autoimmune diseases. At best, the specification provides a link from the composition comprising 46 specific *Clostridia* from clusters IV and XIVa to the upregulation of specific T regs in the intestinal lamina propria. However, the specification provides no causative link between this localised upregulation of T regs and the treatment of autoimmune or allergic diseases as is currently generically claimed.

(61) Two very significant extrapolations are required to arrive at the claimed subject-matter from the technical information provided in the patent:

- i. From experiments on colitis (a gut autoimmune disease) to any autoimmune disease; and
- ii. From data on a combination of 46-strains – none of which are actually identified as being *Clostridium spp.* – to any single strain or any combination of strains provided that they are in the genus *Clostridium*.

(62) Firstly, the OD erred in stating that identifying whether a particular bacteria was of the taxonomic genus *Clostridium* was a routine matter at the effective date of the claims. As stated in D68, page 50, right hand column, 1st paragraph:

“The situation is even more complicated by the present inability to define a genus Clostridium...”

(63) Thus, the skilled person would not be sure whether any particular strain of bacteria fell, or now falls, within the scope of the claims. The changing make-up of the taxonomic genus *Clostridium*, with bacteria routinely reclassified into different genera over time as explained in D22, D54, D68 and D74. The meaning of the term “genus *Clostridium*” in a taxonomic sense therefore changed over time, including different strains of bacteria at each priority date, the filing date and now in the present.

(64) Experimental evidence is provided in D20 and D23, discussed in detail below, that a combination of several *Clostridium* strains (i.e. significantly more than is required by the claims, which encompass a single strain) was **unable** to induce the accumulation of FoxP3 Tregs, and that with the exception of only two unidentified strains, no single strain of *Clostridia* alone can induce the proliferation or accumulation of Foxp3+ T regs. Far from being “isolated failures” as referenced by the OD in section 8.3.3 of the decision, the number of failures in D20 and D23

significantly outweighs the isolated examples where Foxp3+ T regs can be induced to accumulate or proliferate. This confirms that the extrapolation, from the limited data in the patent to the claim scope, is implausible.

(65) The patent also suffers from an insufficiency in its teaching regarding the requirement for the bacteria from the genus *Clostridium* to induce **proliferation or accumulation** of regulatory T cells in the individual. The patent does not enable the skilled person to determine whether regulatory T cells have been induced to **proliferate**. There is certainly no information in the patent as to how to determine a therapeutically relevant level of proliferation or accumulation of Foxp3+ Tregs.

(66) These failings are discussed in more detail below – all the while bearing in mind that for the claims to be enabled according to the interpretation of the OD, it must be unambiguously shown that the strain of bacteria inducing the proliferation or accumulation of Foxp3+ Tregs is from the taxonomic genus *Clostridium*.

(67) The Board of Appeal in D67 agreed that disclosure relating to the 46-strains of *Clostridium* in the patent **does not provide the skilled person** with an enabling disclosure regarding individual components of that 46-strain combination. This can be seen in the second half of paragraph 42 and in paragraph 43 of D67:

In particular, the board is inclined to agree with opponent 1 that the disclosure in the application relating to the 46-strains of *Clostridium* does not provide the skilled person with any knowledge that it is clusters IV and XIVa members of the genus *Clostridium* that are eliciting the effect seen in the application (see Ol's statement of grounds of appeal, point 54).

(68) The Board's opinion goes on, in paragraph 43, to reiterate that (emphasis added) “*any effects disclosed in the application for the composition of 46 strains cannot be attributed to bacteria of the genus *Clostridium* of the two relevant clusters, IV and XIV, alone*”.

(69) The disclosure of a particular 46-strain combination is therefore limited to that combination – and cannot be extrapolated to individual components of that combination. The patent does not test, and does not demonstrate or otherwise make it credible, that each strain or even a representative proportion of strains within the 46-strain combination provides a therapeutically-effective FoxP3+ Treg inducing effect. It certainly does not make credible that other strains of bacteria of the genus *Clostridium*, outside of that 46-strain combination, will provide the same effect.

(70) The Board's opinion in the parent case therefore supports our objection that the patent does not enable the current claim that *any* bacteria of the genus *Clostridium* can induce FoxP3+ Tregs, let alone to a therapeutically-relevant level as required by the claims.

7.2 Lack of a plausible disclosure of the claimed therapies

(71) The data in the patent are very difficult to reconcile with the claimed subject-matter, such is the gulf between the technical disclosure of the patent and the claims.

7.2.1 Summary of the data in the patent

(72) A detailed review of the substantial data in the patent reveals that the experiments relate to a single combination of 46 strains of *Clostridium* spp., while colitis is the only disease that is modelled. The Examples sit in six conceptual groups.

(73) It's important to break down these groups of Examples. As will be shown below when the data are analysed, all that the Patentee has demonstrated is to explain some of the mechanisms behind a prior disclosure that a 46-strain combination of *Clostridium* has a beneficial effect. The tests on mechanisms do not relate directly to *Clostridium* bacteria in general and do not test other sources or combinations of *Clostridium* bacteria. It is not even clear exactly which strains are present in the 46-strain combination. The only information relating to a smaller fraction of bacteria is that Cluster IV alone has a lesser effect than the 46 strain combination. That is of course not a surprising result.

(74) The only investigation of *Clostridium* bacteria other than the 46-strain combination comes in Example 18, which merely observes that high amounts of spore-forming bacteria, such as *Clostridium* clusters XIVa and IV, are found in faeces. There is no evidence, anywhere in the patent, that substantially any *Clostridium* will providing a therapeutic effect.

(75) It was already known in the art (e.g. D2, D24) that decreases in certain *Clostridium* clusters have been reproducibly reported in the gut of IBD patients and are thus probiotic candidates for the treatment of IBD. It was also known from D2 that *Clostridium* cluster IV bacteria *Faecalibacterium prausnitzii* was able to induce IL-10 production in the colon and thereby treat autoimmune disorders of the colon such as Chron's disease (CD).

(76) The data in the specification therefore do not justify the extreme breadth of the claims.

Examples 1 to 9 – Gram positive Chloroform resistant *Clostridium* may influence Tregs

(77) Example 1 investigates whether accumulation of regulatory T cells in the colonic lamina propria was dependent on commensal bacteria, in mice maintained in the absence of specific pathogens (Specific Pathogen Free "SPF" mice). Tregs were observed to be present at high frequency in the lamina propria (LP) of the gastrointestinal tracts (in particular the colon) and increase up to three months after birth, whereas peripheral lymph node (PLN) Tregs remain constant after two weeks.

(78) Example 2 investigates whether the temporal Treg (CD4⁺/FoxP3⁺) accumulation in the colon had a relationship with commensal microbiota. Tregs are seen to be increased in the colon of SPF mice compared to Germ-Free (GF) mice, and treatment of SPF mice with antibiotics correlates with a decrease in colonic Tregs. These data show that only colonic LP Tregs increase and decrease in correlation with commensal bacteria.

(79) Example 3 administers faeces from SPF mice to GF mice, observing that after three weeks Tregs increase only in the colonic LP of the resulting “converted” mice.

(80) Experiments 1 to 3 therefore suggest an association, in mice, between commensal bacteria and Tregs in the **colonic LP only**. The **effect is not seen in the PLN or the Small Intestine (SI) LP**.

(81) Example 4 investigates the colonic LP further. The Treg ratio is shown to increase (although not significantly) when LP signalling is obstructed, suggesting that the decrease in colonic LP Tregs that was observed in the GF and antibiotic mice does not result simply from disorganised gut-associated lymphoid tissues but is likely caused by the absence of bacterial-associated specific signals.

(82) Example 5 investigates whether a specific intestinal flora induced the colonic Treg accumulation. It is observed that Tregs decrease in the colon when vancomycin is administered to SPF mice, but not when polymyxin is administered, suggesting that Gram-positive commensal bacteria played a role in the accumulation of Tregs.

(83) Example 6 begins by referencing Gaboriau-Rothiau et al (D1), noting that this prior art suggests that spore-forming bacteria play an important role in the intestinal T-cell response. Following this prior art disclosure, Chloroform-resistant faecal microorganisms were orally administered to GF mice, and it was observed that intestinal Tregs increased. This aligns with the disclosure of Gaboriau-Rothiau et al (D1).

(84) Example 7 sought to identify the species of intestinal microbiota that induced accumulation of Tregs in Examples 4 to 6. A number of known microorganisms were orally administered to GF mice. It was observed that Bacteroides increase colonic LP Tregs modestly, and a **(known)** 46-strain combination of Clostridium increases the colonic Tregs by a larger amount. Segmentous Filamentous Bacteria (SFB) provided no effect. The effect was again limited to colonic LP, and **no effect was seen in SI LP**. Importantly, the 46-strain combination of Clostridium was chosen because it has already been shown, in Itoh (D8) that this combination is present in faeces of limited flora mice and has an effect on caecal size in GF mice. There is therefore nothing new in the selection of this combination of 46 strains. There is no delineation of the effects of particular strains within this large combination.

(85) Example 8 analysed CD4, Foxp3 and Helios expression in colon and thymus LP lymphocytes of various mice, with results showing that Clostridium and SP free mice have significantly higher Helios negative Foxp3 cells than GF or Lactobacillus mice, i.e. most Tregs in Clostridium-colonised and SPF mice are Helios negative. Helios was thought to be a marker for

thymic-derived Tregs, so this is said to suggest that the SPF and clostridia mice Tregs were **induced in the periphery**, i.e. so-called iTreg cells.

(86) Example 9 investigates whether the *Clostridium* spp. have an influence on other T cells. Again, the same (known) **46 strain network** of *Clostridium* spp. was compared to SFB, 16 strains of *Bacteroides* and SPF microbiota. Colonic LP lymphocytes were isolated and stimulated with PMA and ionomycin, intracellular IL-17 and IFN- γ stained and the ratio of IFN- γ + or IL-17+ cells in CD4+ analysed. Clostridia had no effect on Th1 (IFN- γ) cells and a slight, non-significant increase in Th17 (IL-17) cells. The suggestion is that **Clostridium specifically induce colonic CD4+ Tregs** and not CD4+ Th1 or CD4+ Th17 T cells.

(87) In summary, Examples 1 to 9 demonstrate that: Tregs are present at high frequency in the lamina propria; colonic LP Tregs increase in correlation with commensal bacteria; there is an association, in mice, between commensal bacteria and Tregs in the **colonic LP only**; Treg increase is likely to be caused by specific signals; Gram-positive commensal bacteria played a role in the accumulation of Tregs; chloroform-resistant (spore-forming) faecal microorganisms play a role in Treg increase; a 46-strain combination of *Clostridium* increase colonic LP Tregs (only); SPF and *Clostridium* mice Tregs were **induced in the periphery**; and the induction is Treg specific.

(88) There is nothing in this first set of experiments that relates directly or closely to the claimed subject-matter. The most relevant data are limited to a specific 46-strain combination of *Clostridium* and there is no model of a disease within the claim scope. These data confirm what was already known (e.g. from D1) – that spore-forming *Clostridium* modulate Tregs. All of the data are in mice.

Examples 10 to 14: Investigating the mechanism of Treg regulation.

(89) Example 10 is the first of a series of experiments that focus on cytokines that may play a role in regulation of regulatory T cells, and association of those cytokine-producing cells with immunosuppressive activity.

(90) The introductory comments to Example 10 note that it was previously reported that **46 strains of *Clostridium* spp exert an influence on the accumulation of CD8+ (CTL) intestinal tract intraepithelial lymphocytes (IELs)**, and that “*it is conceivable that Clostridium regulates the immune system in various aspects*”. This is further evidence that there are myriad potential effects of *Clostridium* on a homeostatic immune system *in vivo*, and it is not possible to conclude that a measure of one cell type, e.g. Tregs, provides a “*surrogate for therapeutic efficacy*”.

(91) Example 10 examines whether colonisation of *Clostridium* provided a colonic environment rich in TGF- β . Whole colons of GF mice, 46-strain *Clostridium*-colonised mice and *Lactobacillus*-colonised mice were cultured for 24 hours and the culture supernatants analysed. It is observed that the amount of TGF- β produced in the colon increased in *Clostridium*-colonised mice. Intestinal epithelial cells of GF and *clostridium*-colonised mice were then cultured, and TGF- β observed only in the *clostridium*-colonised mice. Splenic CD4+ cells were then cultured for five

days with a 50% CM in which IECs from GF or Clostridium-cultured mice had been cultured, plus anti-CD3, and with or without anti-TGF- β . Foxp3 expression was detected, and it was observed that the Clostridium-cultured IEC supernatant CD4⁺ cells show increased FoxP3 expression compared to GF-cultured, and that this FoxP3 expression decreased significantly upon addition of anti-TGF- β . The Example concludes that this indicates that the supernatant of Clostridium-cultured IECs accelerated **differentiation** into FoxP3-expressing cells, which differentiation was inhibited by anti-TGF- β . This is merely mechanistic detail; the claims do not require or relate directly to TGF- β .

(92) Next, expression of MMP2, MMP9 and MMP13 (thought to contribute to activation of latent TGF- β), and IDO (thought to be involved in induction of Tregs) in the IECs was examined. Yet again, the known **46 strains of Clostridium spp.** or three strains of lactobacillus were tested, this time orally administered to GF mice. IECs were collected after three weeks and expression determined by RT-PCR. Three mice (only) per group were analysed and increases in each tested gene observed. Clostridium is said to activate the IECs and led to the production of TGF- β and other Treg inducing molecules in the colon.

(93) Example 11 tests whether the Treg accumulation induced by the Clostridium colonisation was dependent on activation of PAMPRs, with the data suggesting that it is not.

(94) Example 12 notes that intestinal tract FoxP3⁺ Treg cells **are known** to exert some immunosuppressive functions through IL-10 production, and that some animals having IL-10 deficient FoxP3⁺ cells are known to develop IBD. CD4 and venus (IL-10) expression was determined in lymphocytes from various tissues of SPF IL10^{venus} mice. The expression of TCR- β chain on colonic LP lymphocyte cell surfaces was also determined, and colonic LP lymphocytes stimulated with PMA and ionomycin then stained for IL-17, IL-4 and IFN- γ . Further, Foxp3 positive and negative CD4 cells were isolated from FoxP3 reporter mice spleens, and venus⁺ cells isolated from the colonic LP and SI LP of IL10^{venus} reporter mice. Expression of predetermined genes was analysed. These data show that SPF mice contain almost no or few IL-10 producing cells in most tissues, but many IL-10 producing cells in lymphocytes from SI-LP and colonic LP. Most of the IL-10 producing cells in the SI and colonic LPs were CD4⁺ and TCR- β ⁺. IL-10 producing CD4⁺ cells expressed FoxP3 and other Treg markers such as CTLA4 and GITR. However, the IL-10-producing CD4⁺ T cells show no phenotypes of Th2 (IL-4 producing) or Th17 (IL-17 producing) cells. This appears simply to confirm that IL-10 correlates with Tregs **in the colon**. Clostridium bacteria are not tested.

(95) Example 13 investigates the IL-10 venus⁺ cells of Example 8 and indicates that the SI LP was rich in Tr1-like cells and the colonic LP cells were “Double Positive” in the colon of SPF mice. IL-10 was not observed in other cells, even though FoxP3 was – demonstrating that outside of the colon, IL-10 is not a suitable proxy for FoxP3⁺ Treg induction and furthermore that the induction of Foxp3⁺ Tregs outside of the colon does not have the same effect on cytokine production as in the colon. All Treg fractions in the colon decreased under GF conditions, and a decrease observed in SPF Venus mice treated with antibiotics. These data show that the genus Clostridium colonised in the colon or a physiologically active substance derived from the bacteria

provides a signal for inducing the accumulation of IL-10+ Tregs in the colonic LP or the expression of IL-10 in T cells.

(96) Example 14 investigates whether the IL-10 producing (venus+) cells induced by the **46 strains of Clostridium spp.** had immunosuppressive function similar to venus+ cells in the colon of SPF mice. CD4+ Effector T cells from the spleen were cultured with APCs subjected to irradiation, anti-CD3 antibody and “a lot” of Treg cells, and tritiated thymidine for the final 6 hours. The data show that proliferation of effector cells decreases as Tregs are added, with the greatest reduction seen for splenic Tregs from FoxP3 reporter mice and similar reductions seen for colonic LP Tregs from mice in which Clostridium were colonised.

(97) The mechanistic investigations of Examples 10 to 14 indicate the potential mechanisms underlying the modulation of Tregs that was known in the art. **Examples 10 to 14 relate to the specific 46 strains of Clostridium spp. There is no model of any particular disease. Examples 10 to 14 show that Foxp3+ IL-10+, Foxp3+ IL-10- and Foxp3- IL10+ cells are present in different amounts, and in different locations.**

Examples 15: Mouse models of colitis

(98) Example 15 is the **only example of a disease model: two mouse models of colitis.** The effect of “the Clostridium” is investigated. This appears to be the same **combination of 46 strains** was investigated in previous examples. It is shown that several measures of colitis are improved after inoculation with a large number of Clostridium.

(99) This effect is limited to the 46-strain combination that is tested. It does not show that any single Clostridium, or any other combination of strains of Clostridium, might also be provide the observed effect.

(100) In section 8.5.1 of the decision, the OD wrongly classified this example as providing data relating to a systemic induction of FoxP3+ Tregs. The data in this example relate to symptoms of colitis, which may be ameliorated by localised treatment of colonic inflammation.

(101) Example 16: IgE production

(102) Example 16 tests the influence of Clostridium colonisation on IgE production and the resultant production of IL-10. Example 16 does not refer to the measurement of Foxp3+ Tregs. Mice were immunised with alum-absorbed ovalbumin, sera collected and levels of Ova-specific IgE tested. In addition, splenic cells were collected and IL-4 and IL-10 production by in vitro OVA restimulation investigated. The IgE level is shown to be lower in Clostridium-abundant mice, IL-4 production is lowered and IL-10 increased **in the splenic cells**. The conclusion is that this indicates that induction of Treg cells by Clostridium in the colon plays an important role in the local and systemic immune response. Yet again, this **does not indicate or make credible that any single Clostridium species or strain, or any particular combination of Clostridium, would also provide this effect, nor is there any demonstrable link to Foxp3+ Tregs –**

particularly given the results of Example 13 that show that outside of the colon IL-10 production was not linked to the presence of Foxp3+ Tregs.

Example 17: Multiple strains of Cluster IV may play a role in FoxP3 expression.

(103) Example 17 assesses colonic FoxP3+ Treg cells in GF mice colonised with **three strains of cluster IV** (strains 22, 23 and 32). An increase in FoxP3+ expression was observed, which was **less than observed for the 46 cluster combination, and which effect on Tregs is not statistically significant (Figure 50)**. This is exactly **as would be expected**, that part of the combination provides part of the effect. These data are not from a disease model and do not indicate whether that significantly reduced effect provided by three strains of one Cluster might be therapeutically relevant. These data also provide no guidance at all whether a single strain or two strains of Cluster IV might have any effect, let alone whether any single strain or species from a different Cluster would provide that effect.

(104) The greatly reduced effect on FoxP3+ Tregs provided by a reduced number of strains means that it is highly doubtful that any and all combinations of strains, or even any single strain, will provide the effect observed for all 46-strains.

(105) Accordingly, these data do not make it plausible that any single species or strain of the genus Clostridium, or any combination of species in combination, are able to induce regulatory T cell proliferation or accumulation and have a beneficial therapeutic effect, in the absence of the other Clostridium in the 46-strain combination.

(106) Furthermore, although three strains named “22, 23 and 32” are tested in combination in Example 17, this appears to be internal nomenclature used by the inventors that does not have any generally recognisable meaning. Figure 49 presents these strains on a phylogenetic tree, but it is far from clear from the disclosure of the patent whether the skilled person could recreate that tree without undue burden and select the same three strains to provide the effect seen in Example 17. It is also far from clear what taxonomic name strains 22, 23 and 32 have.

Example 18: Chloroform-resistant human faecal sample includes Clusters XIVa and IV

(107) Finally, Example 18 investigates whether a chloroform-resistant fraction of a faecal sample **from humans** (as known from **D14**) had the effect of inducing proliferation or accumulation of Tregs similar to the chloroform-resistant fraction of the mice faecal sample. Human chloroform-resistant faecal bacteria were inoculated into GF mice. After three weeks the colons of the mice were analysed for CD4 and FoxP3 expression, and an increase in FoxP3 expression observed in the colonic T cells in human spore-forming-bacteria colonised mice. This is not specific to Clostridium. Further, these data show an increase of expression but do not demonstrate that proliferation has been induced.

(108) Example 18 then investigates which species grew in the mice gavaged with chloroform-treated human stool. Bacterial DNA was isolated from a healthy human volunteer or

faecal pellets from GF mice gavaged with the chloroform-treated human stool. These data show that stool from the gavaged mice exhibit high amounts of spore-forming bacteria, **such as** Clostridium clusters XIVa and IV, and a decrease in non-spore-forming bacteria. The data on other clusters are not shown. Further, these are **separate assays** of the presence of the two clusters. There is no evidence, anywhere in the patent, of the combination of Clusters IV and XIVa providing an effect.

7.2.3 There is no evidence in the patent that bacteria from the genus Clostridium, in general, can be expected to induce Tregs to a therapeutically relevant level

(109) The claim requires that essentially any bacteria from the genus Clostridium will provide the claimed therapeutic effect. This includes any single strain, or any combination of strains. However, there is no evidence in the patent that the claimed therapeutic effect is provided by bacteria from the genus Clostridium as a general class.

(110) A known combination of 46 spore-forming strains of Clostridium is used in the Examples of the patent. These 46 spore-forming strains of Clostridium were isolated from a chloroform-resistant fraction of mouse faecal microorganisms, as described in D8. The exact content of this 46-strain combination is not disclosed, although they are referred to (e.g. in Example 7) as “Clostridium spp.”. The lack of a reproducible breakdown of the contents of the 46-strain combination means that no breakdown of the technical teaching is possible. The use of the 46-strain combination is thus a unitary and indivisible teaching.

(111) The patent does not test, and does not demonstrate or otherwise make it credible, that each strain or even a representative proportion of strains within the 46-strain combination provides a therapeutically-effective FoxP3+ Treg inducing effect. It certainly does not make credible that other strains of bacteria of the genus Clostridium, outside of that 46-strain combination, will provide the same effect.

(112) A subset of three strains from the 46 strain combination is tested once in Example 17. This very simple experiment is not a disease model, and merely shows that a much **lower** effect on colonic FoxP3+ Tregs is associated with these three strains than for the larger combination of 46 strains. The greatly reduced effect on FoxP3+ Tregs provided by a reduced number of strains means that it is highly doubtful that any and all combinations of strains, or even any single strain, will provide the effect observed for all 46-strains.

(113) Although the three spore-forming strains of Clostridium spp. named “22, 23 and 32” (“Cluster IV” strains) are tested in combination in Example 17, this appears to be internal nomenclature used by the inventors that does not have any generally recognisable meaning. Figure 49 presents these strains on a phylogenetic tree based on 16S rRNA sequencing, but it is far from clear from the disclosure of the patent whether the skilled person could recreate that tree, and so identify strains “22, 23 and 32” without undue burden and select the same three strains to repeat Example 17. Again, the patent does not provide a granular disclosure that would allow conclusions to be drawn regarding the role of *different* bacteria from the genus Clostridium, and

so determine the effects of any and all bacteria of the genus *Clostridium*. All that this discloses, is that a subset of the 46-strain combination provides a lower effect, thereby emphasising the need for the whole 46-strain combination.

(114) The claim extends to the use of any *Clostridium* bacteria, yet the technical disclosure of the patent is limited to a specific combination of 46 spore-forming strains. These 46 strains are themselves not clearly and fully disclosed.

(115) The failure to demonstrate that **substantially any** *Clostridium* bacteria, whether a single species, strain or Cluster, or various different combinations of species, strains or clusters, means that it is not plausible that any and all *Clostridium* bacteria will provide the claimed effect. The patent only exemplifies a specific mixture of 46 spore-forming strains of *Clostridium* spp. The claims are not limited to this 46-strain combination, and are not even limited to spore-forming bacteria.

(116) The skilled person is left to perform a research project to test each and every *Clostridium* species, cluster or strain, and combination thereof, to try and determine if or how it might be put in to effect.

(117) Notably, the Patentee has obtained other patents in this family with claims requiring that the *Clostridium* bacteria are specifically from Clusters IV and/or XIVa. In the granted grandparent EP 2,575,835, the claims require *Clostridium* from Clusters IV and XIVa. In the granted parent case EP 3,178,483, and in the in the sister divisional EP 3,552,613, the claims require *Clostridium* bacteria from Clusters IV and/or XIVa. In those cases, the Patentee relies on the data in the patent allegedly showing that *Clostridium* bacteria specifically from Clusters IV and XIVa provide the claimed effect. In the Patentee's Grounds of Appeal on EP 2,575,835 filed on 5 August 2019, paragraph 6 asserts that the invention is *"the breakthrough insight that bacteria of 'Clostridium clusters' IV and XIVa have a specific effect upon patients' immune systems"*. The Patentee therefore considers the technical contribution to be the specific bacteria from Clusters IV and XIVa. Yet, in the current case, they assert that a much broader claim is appropriate.

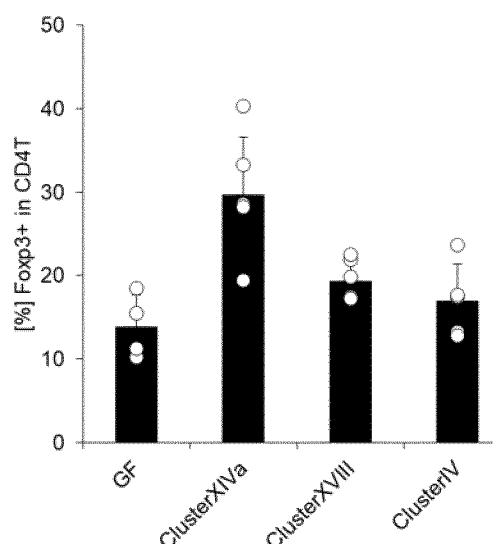
(118) During prosecution of the present application, the Examining Division (in its exam report of 21 August 2019) strongly doubted whether essentially all bacteria of the genus *Clostridium* will provide the observed effects, and asserted that *Clostridium* Clusters IV and/or XIVa are necessary to achieve the alleged effect.

(119) While we disagree that Clusters IV and XIVa are sufficiently described, the Examining Division was certainly correct in its view that it is not credible that essentially all and any bacteria of the genus *Clostridium* will provide the effects observed for the 46-strain combination of spore-forming *Clostridium*.

(120) In reply to this objection, the Patentee's letter of 25 November 2019 at page 3 asserted that *"the initial, key breakthrough was to associate gut bacteria of the 'Clostridium' type with the induction of FoxP3+ Tregs"*. This is a different position from that taken by the Patentee noted

above, when defending EP 2,575,835, that the invention allegedly lies specifically in clusters IV and XIVa.

(121) The Patentee's letter of 25 November 2019 included a graph allegedly showing that "bacteria" of only Cluster XVIII also have the effect of inducing FoxP3+ Tregs. This graph is pasted below for ease of reference:



(122) This post-filing evidence cannot be relied upon because the application as filed did not make the claimed subject-matter plausible. Post-filing data regarding "Cluster XVIII" are irrelevant because the **patent does not even mention Cluster XVIII**.

(123) Furthermore, Figure 49 of the patent **does not mention that** Cluster XVIII strains are even **present in the 46-strain combination** of spore-forming Clostridium that is exemplified in the patent. Therefore, Cluster XVIII is neither mentioned nor suggested as part of the technical disclosure in the patent, and there is no credible technical link between the data in the patent and the post-filing graph relating to Cluster XVIII provided by the Patentee. Accordingly, the graph relating to Cluster XVIII provided by the Patentee is not a "*confirmatory experiment*" as asserted by the Patentee. It is the **first presentation of this information**, and as such cannot confirm anything in the patent.

(124) The graph provided by the Patentee on 25 November 2019 (pasted above) does not include any statistical analysis and it would appear that the error bars for at least the Cluster IV-administered and Germ Free mice overlap, indicating that Cluster IV Clostridium does not have a significant effect on FoxP3+ Tregs. The error bar for the Cluster XIVa group also appears to be very large. These large error bars may explain the lack of statistical analysis and lack of indicated significance (e.g. an asterisk) in the graph. Furthermore, this graph does not indicate in which mice and cells the FoxP3+ measurements were made, so it is not possible to draw any firm conclusions.

(125) Therefore, the Examining Division was right to object that is not credible from the application as filed that essentially all and any bacteria of the genus Clostridium will provide the

effects observed for the 46-strain combination of spore-forming Clostridium. The unreliable evidence provided by the Patentee in reply does not cure that failing in the disclosure of the patent. The OD erred in deciding otherwise.

7.2.4 Evidence that the claimed bacteria do not provide the claimed mechanistic effect

(126) It is not plausible that the claimed effects are provided by any or all bacteria of the genus Clostridium. There is therefore only a weak presumption that the claimed invention is enabled (T63/06), which can be rebutted with evidence.

(127) Evidence is provided below that most of the claimed uses cannot be provided. The OD was incorrect to characterize the weight of evidence of non-working embodiments as “isolated” in section 8.3.3 of the decision.

(128) **D20** is an expert declaration provided by the Patentee on a related US patent application (US Patent application number 15/487,533, cited as **D20a**). **D20** tests three combinations of Clostridium bacteria. All of these combinations comprise several Clostridial clusters. **D20b** summarises the data in **D20a** as discussed in **D20**.

(129) The results are reported in paragraph 10 of D20, which reports that a mixture of 17 different strains of Clostridium bacteria (Cluster XVIII x2, Cluster IV x2, Cluster XIVa x12, Cluster XVI) and a mixture of 11 different strains (XIVa x9, IV, XVIII) are each able to induce the proliferation of colonic Tregs when provided in combination. However, the mixture of six strains of Clostridium present in the 17-mix but absent from the 11-mix was **unable to induce proliferation of colonic Tregs**, despite containing **six different strains of bacteria from the genus Clostridium** (one strain from each of clusters IV, XVI and XVIII, and three strains from XIVa):

10. A graph showing the results of the study is shown in Exhibit B. Briefly, both the 11 mix and 17 mix were effective in promoting a statistically significant accumulation of colonic lamina propria Foxp3+CD4+ T cells, as assessed by quantifying the number. In contrast, the 6 mix did not significantly induce the accumulation of colonic lamina propria Foxp3+CD4+ T cells.

(130) D20 therefore provides evidence that **only specific combinations** of strains from **certain clusters of Clostridia** (from the genus Clostridium) are capable of inducing the proliferation or accumulation of colonic Foxp3+ Tregs.

(131) It is therefore very clear that many bacteria from the genus Clostridium, when tested in the hands of the Patentee, do not provide the alleged mechanism that underlies the claimed treatment of autoimmune and allergic diseases.

(132) D23 provides even further evidence that the majority of bacteria from the genus Clostridium, when used alone, do not induce any significant level of Foxp3+ Tregs at all, let alone to a clinically significant level. D23 states that Foxp3+ Tregs are induced by a **rationally selected** subset of 17 strains of clostridia within clusters IV, XIVa and XVIII. Notably, as

commented at paragraph (44) of our Notice of Opposition, the **patent does not even mention Cluster XVIII**.

(133) The facts on file, particularly as published by the patentee, therefore demonstrate that rational selection of specific strains of Clostridia is necessary to achieve the induction of Foxp3+ Tregs. It is an unguided research project to determine which can achieve this initial effect. Even the induction of Foxp3+ Tregs is not enough to satisfy the claim requirements, because the claim relates to a proposed downstream effect of this induction of Foxp3+ Tregs – alleged treatment of any autoimmune or any allergic disease. The classes of diseases that are alleged to be treated by the present claim to any composition containing any strain of Clostridium are vast and have very differing aetiologies. There is no plausible way that all, or even a majority, of autoimmune and allergic diseases can be treated with the claimed compositions or by the claimed mechanism.

(134) Figure S6 from D23 is reproduced below:

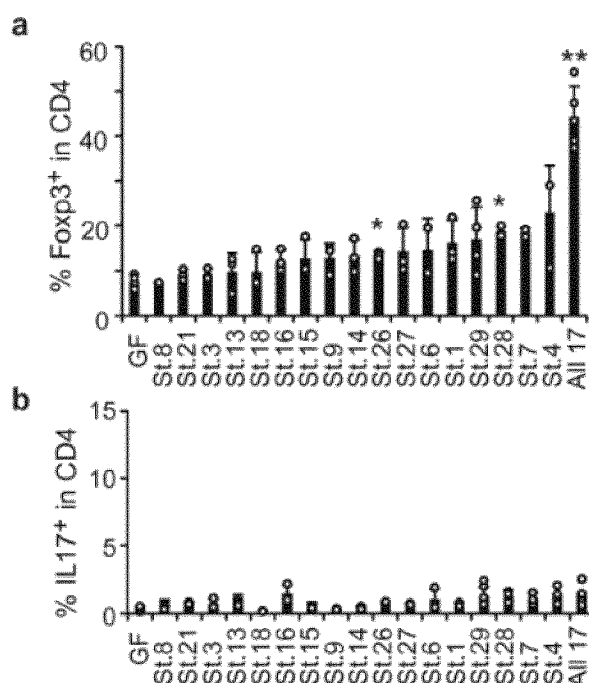


fig. S6 Treg induction capability of each strain. Percentages of Foxp3⁺ cells (a) and IL-17⁺ cells (b) in the CD4⁺ cell population in colonic lamina propria of IQ1 exGF mice monocolonised with each of the 17 strains. Circles represent samples from individual animals. Error bars, s.d. ***P* < 0.01; **P* < 0.05 vs. GF, as calculated by Student's *t*-test.

(135) Of the 17 strains tested, only 2 were able to induce accumulation or proliferation (which, it is not clear) of Foxp3+ cells to a level that was significantly different from the level induced by the negative control of GF mice. This is important for two reasons.

(136) Firstly – the vast majority of the specifically, rationally selected strains, chosen for the presumed ability to provide a clinical effect could not induce the proliferation of Foxp3+ Tregs unless they were provided as part of a mix of 17 strains. This further supports the data in D20 and the patent, which both point to only specific combinations of bacteria from Clostridium

Clusters IV and XIVa being able to induce the proliferation or accumulation of Foxp3+ Tregs. The data in Figure S6a directly contradict the assertion of the OD in section 8.3.2 that the “best” strains of Clostridium from D23 support the claimed mechanism of action. The OD identified strains 28, 7 and 4 as the “best” strains – despite strains 7 and 4 being statistically no different to the GF mice.

(137) Secondly – the negative control used was GF mice. It was already known that any commensal bacteria introduced into a GF mouse will have a disproportionately large impact as compared to introducing the same bacteria into a wild-type mouse. Therefore, the induction of Foxp3+ Tregs in GF mice cannot support a clinically significant effect in a patient population.

(138) It is clear, therefore, that the OD erred in its analysis of the data in D20 and D23 in important ways. The OD wrongly considered that Figure S6 of D23 provided evidence of general success in the induction of Foxp3+ Tregs by specific strains of Clostridia, rather than providing evidence that of the 17 individual strains tested, only 2 produced a significant effect, and of the 5 combinations tested, as shown in Figure 3c only the 17 mix induced a significant increase the frequency of Foxp3+ Tregs in the colon. Combined with the data in D20, this shows a convincing picture of some isolated successful combinations (the 17 mix, 11 mix and 46 mix), amongst a much larger number of failures. It is therefore very clear that many bacteria from the genus Clostridium, when tested in the hands of the Patentee, do not provide the alleged mechanism that underlies the claimed treatment of autoimmune and allergic diseases.

7.2.5 It is not plausible that the claimed diseases can be treated by the claimed mechanism

(139) Even if the patentee had shown, which they have not, that in general bacteria from the genus clostridium can induce the induction of Foxp3+ Tregs, the induction of Foxp3+ Tregs is not enough to satisfy the claim requirements, because the claim relates to a proposed downstream effect of this induction of Foxp3+ Tregs – alleged treatment of any autoimmune or any allergic disease. The classes of diseases that are alleged to be treated by the present claim to any composition containing any strain of Clostridium are vast and have very differing aetiologies. There is no plausible way that all, or even a majority, of autoimmune and allergic diseases can be treated with the claimed compositions or by the claimed mechanism. The OD was incorrect in section 8.5.6 of the decision to state that the patent makes it plausible that the claimed composition has a direct effect on the mechanism underlying all autoimmune and allergic diseases.

(140) It is completely implausible that autoimmune diseases in general can be treated, or that allergic diseases in general can be treated, specifically by the induction of accumulation or proliferation of Foxp3+ T Regs by bacteria from the genus Clostridium. In section 8.5.6 of the decision, the OD stated that the data in the patent had plausible shown that the claimed compositions had a direct effect on a mechanism specifically involved in the claimed diseases. This is clearly incorrect, as to date there is still no plausible mechanism linking the induction of colonic Foxp3+ Tregs to the treatment of all autoimmune and allergic disease.

(141) For example, Type I Diabetes and Psoriasis are both generally accepted to be autoimmune diseases, but it is not plausible that these very diverse conditions will be treated by the same therapy or that either could be treated by Clostridium. The patent actually goes much further and states on page 32 that diseases that can be treated include **Parkinson's disease and Alzheimer's disease**. Bearing in mind that Herculean research efforts and tens of billions of dollars have so far failed to provide a single therapy for Alzheimer's and Parkinson's, the patent's recital that these diseases can be treated highlights the **lack of plausibility across the claim scope**.

(142) It is also problematic that the disease mechanisms and causes of many autoimmune diseases is not known, are almost certainly different for the different diseases listed in the patent and will involve different immune functions in different disease states. The requirement for a plausible disclosure requires that the patent *"provides some information in the form of, for example, experimental tests, to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se"* (T609/02).

(143) This requirement **cannot be met** in the current case, where the metabolic mechanism of action specifically involved in many of the claimed diseases **is not known**, and the patent provides no information at all regarding the particular disease. An alleged effect on a particular subset of colonic Tregs cannot be enough, because it is not known whether these cells are specifically involved in many of the claimed diseases. For example, the disease mechanism for multiple sclerosis may involve demyelination by the immune system or failure of myelin-producing cells. Furthermore, any T cell component of CNS disease – such as MS, Alzheimer's or Parkinson's, will be mediated by T cells at the site of disease.

(144) Only murine models of colitis are tested in the patent. There is no disease model of allergy, and furthermore Example 16 is silent about Foxp3+ Tregs.

(145) The current data only relate to Tregs induced in the colon, and so provide little useful information on complex diseases in distant, distinct tissues, perhaps mediated by thymically-derived nTregs.

(146) It is far from clear whether the induced Tregs ("iTregs") that are identified in the mouse experiments of the patent, have the same suppressive functions *in vivo* as natural Tregs. This is difficult to establish in humans (and the mice data on iTregs does not change this deficiency).

(147) Furthermore, the data indicate an effect on iTregs that is **restricted to cells in the colonic Lamina Propria**. The effect of the Clostridium on the Tregs is even demonstrated (at Example 10) to be **mediated by the host's colonic Intestinal Epithelial Cells** (IECs). It is not at all clear whether a similar effect could be achieved at other sites in the body, in particular non-epithelial tissues in other organs. The identification of iTregs in mice Colonic Lamina Propria is therefore of extremely limited clinical relevance, and **only provides a teaching of potential relevance to disorders of the colon in which iTreg imbalance plays a role**.

(148) These limited data are not enough to predict whether the *Clostridium* will have a therapeutic effect on different Tregs in non-colonic tissues.

(149) Ultimately, a significant problem exists because the patent only tests one disease of the colon, colitis. It is well-known that immune regulation *in vivo* is very difficult to predict based on *in vitro* results, because the *in vivo* immune system is a complex homeostasis that comprises myriad parts that interact and feedback. On the basis of a single colonic disease model in mice, following a series of *in vitro* experiments limited to iTregs in the colon (involving colonic epithelial cells), the Patentee has been granted a claim of implausible scope. However, the test of this solitary colonic disease in a mouse model cannot plausibly enable a claim to the great diversity of all autoimmune diseases and all allergic diseases in humans.

(150) This implausible extrapolation is easily seen when all of the diseases that the patent indicates is within the scope of the claim (at pages 9 and 10 of the patent) is read carefully. **This list of conditions occupies an entire page of the granted patent.** This page is repeated below for ease of reference.

[0028] The composition of the present invention can be used, for example, as claimed as a pharmaceutical composition for preventing or treating an autoimmune disease such as chronic inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, or Hashimoto's disease, or an allergic disease such as pollenosis or asthma. Also disclosed is a pharmaceutical composition for suppressing rejection in organ transplantation or the like; a food or beverage for improving immune functions; or a reagent for suppressing the proliferation or function of effector T-cells.

[0029] Autoimmune diseases, allergic diseases, and rejection in organ transplantations and the like include inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, sprue, autoimmune arthritis, rheumatoid arthritis, Type I diabetes, multiple sclerosis, graft vs. host disease following bone marrow transplantation, osteoarthritis, juvenile chronic arthritis, Lyme arthritis, psoriatic arthritis, reactive arthritis, spondyloarthritis, systemic lupus erythematosus, insulin dependent diabetes mellitus, thyroiditis, asthma, psoriasis, dermatitis scleroderma, atopic dermatitis, graft versus host disease, acute or chronic immune disease associated with organ transplantation, sarcoidosis, atherosclerosis, disseminated intravascular coagulation, Kawasaki's disease, Grave's disease, nephrotic syndrome, chronic fatigue syndrome, Wegener's granulomatosis, Henoch-Schoenlein purpura, microscopic vasculitis of the kidneys, chronic active hepatitis, uveitis, septic shock, toxic shock syndrome, sepsis syndrome, cachexia, acquired immunodeficiency syndrome, acute transverse myelitis, Huntington's chorea, Parkinson's disease, Alzheimer's disease, stroke, primary biliary cirrhosis, hemolytic anemia, polyglandular deficiency type I syndrome and polyglandular deficiency type II syndrome, Schmidt's syndrome, adult (acute) respiratory distress syndrome, alopecia areata, seronegative arthropathy, arthropathy, Reiter's disease, psoriatic arthropathy, chlamydia, yersinia and salmonella associated arthropathy spondyloarthritis, atheromatous disease/arteriosclerosis, atopic allergy, food allergies, autoimmune bullous disease, pemphigus vulgaris, pemphigus foliaceus, pemphigoid, linear IgA disease, autoimmune haemolytic anaemia, Coombs positive haemolytic anaemia, acquired pernicious anaemia, juvenile pernicious anaemia, myalgic encephalitis/Royal Free Disease, chronic mucocutaneous candidiasis, giant cell arteritis, primary sclerosing hepatitis, cryptogenic autoimmune hepatitis, Acquired Immunodeficiency Disease Syndrome, Acquired Immunodeficiency Related Diseases, Hepatitis C, common varied immunodeficiency (common variable hypogammaglobulinaemia), dilated cardiomyopathy, fibrotic lung disease, cryptogenic fibrosing alveolitis, postinflammatory interstitial lung disease, interstitial pneumonitis, connective tissue disease associated interstitial lung disease, mixed connective tissue disease associated lung disease, systemic sclerosis associated interstitial lung disease, rheumatoid arthritis associated interstitial lung disease, systemic lupus erythematosus associated lung disease, dermatomyositis/polymyositis associated lung disease, Sjogren's disease associated lung disease, ankylosing spondylitis associated lung disease, vasculitic diffuse lung disease, haemosiderosis associated lung disease, drug-induced interstitial lung disease, radiation fibrosis, bronchiolitis obliterans, chronic eosinophilic pneumonia, lymphocytic infiltrative lung disease, postinfectious interstitial lung disease, gouty arthritis, autoimmune hepatitis, type-1 autoimmune hepatitis (classical autoimmune or lupoid hepatitis), type-2 autoimmune hepatitis (anti-LKM antibody hepatitis), autoimmune mediated hypoglycemia, type B insulin resistance with acanthosis nigricans, hypoparathyroidism, acute immune disease associated with organ transplantation, chronic immune disease associated with organ transplantation, osteoarthritis, primary sclerosing cholangitis, idiopathic leucopenia, autoimmune neutropenia, renal disease NOS, glomerulonephritides, microscopic vasculitis of the kidneys, discoid lupus, erythematosus, male infertility idiopathic or NOS, sperm autoimmunity, multiple sclerosis (all subtypes), insulin independent diabetes mellitus, sympathetic ophthalmia, pulmonary hypertension secondary to connective tissue disease, Goodpasture's syndrome, pulmonary manifestation of polyarteritis nodosa, acute rheumatic fever, rheumatoid spondylitis, Still's disease, systemic sclerosis, Takayasu's disease/arteritis, autoimmune thrombocytopenia, idiopathic thrombocytopenia, autoimmune thyroid disease, hyperthyroidism, goitrous autoimmune hypothyroidism (Hashimoto's disease), atrophic autoimmune hypothyroidism, primary myxoedema, phacogenic uveitis, primary vasculitis, vitiligo, allergic rhinitis (pollen allergies), anaphylaxis, pet

allergies, latex allergies, drug allergies, allergic rhinoconjunctivitis, eosinophilic esophagitis, hypereosinophilic syndrome, eosinophilic gastroenteritis cutaneous lupus erythematosus, eosinophilic esophagitis, hypereosinophilic syndrome, and eosinophilic gastroenteritis.

(151) In the absence of data in relevant model systems of autoimmune and allergic disease *in vivo*, the extrapolation required to accept that a single colitis example makes plausible the treatment of all of these diseases, is **stretched far beyond breaking point**. It is not plausible that all of these diseases can be treated.

(152) A two-stage extrapolation is therefore required to arrive at the claimed subject matter from the data in the patent. First, it needs to be accepted without any data or evidence that any single Clostridium strain or cluster, or any combination of perhaps a few Clostridium strains can modulate colonic FoxP3+ Tregs, and secondly it must then be accepted without any data or evidence that any such effect in the colon can be translated into an effective treatment for any autoimmune or any allergic disease in any tissue of the body.

(153) Notably, D10 is a contemporaneous journal publication of much of the data in the patent, co-authored by the inventors. This concludes in the final paragraph on page 4 in very speculative, hopeful terms (emphasis added):

*“Because gnotobiotic mice colonized with three strains of Clostridium showed an intermediate pattern of Treg induction between GF mice and mice inoculated with all 46 strains (fig. S19), we **speculate** that a diverse set of metabolites that are most efficiently produced by the **46 strains of Clostridium as a whole** may be required for the optimal induction of Tregs. **Identifying these metabolites and the molecular mechanisms underlying the Clostridium-host crosstalk will provide invaluable information toward understanding how the gut microbiota regulate immune homeostasis and may suggest potential therapeutic options for treating human IBD and allergies.**”*

(154) This conclusion, by the inventors, is cautious and speculative. It clearly states that significant further work is needed even to provide information **toward** understanding how the gut microbiota regulate immune homeostasis.

(155) Importantly, this conclusion is that the 46 strains of Clostridium as a whole may be required, which reinforces that it is not credible that any single Clostridium species or strain, or any combination other than the exemplified 46-strain combination, will provide the effect observed for those 46 strains. The conclusion also only mentions IBD, reinforcing that the teaching does not credibly underpin *any* autoimmune disease.

(156) A very important point to note, is that this journal publication by the inventors includes a number of **experimental results that are not present in the patent**. All of Figures 3A-D, 2B, 4A, S1, S2A, S4, S5, S6, S7A, S7C, S9, S10A-C, S13D, D14, S16, S17 and S18A in D1, are **missing from the patent**. These results include Figures S5, S6, S9 and S18A relating to Clostridium Clusters IV and XIVa, and Figure S17 relating to IL10 expressing CD4+ cells in lung, liver and spleen following Clostridium inoculation. The journal article was published before the filing date of the patent, so the **Patentee chose not to include** all of the available data in the

patent. Accordingly, the patent is a lesser technical contribution than the corresponding journal article.

(157) In summary, the patent lacks data to show any link between individual strains of bacteria from the taxonomic genus *Clostridium* and the induction of Foxp3⁺ Tregs at all, the patent contains limited data relating to a specific 46 strain mix of *Clostridia* that can induce Foxp3⁺ Tregs in the colonic lamina propria only, but not in other parts of the intestines, and contains no data at all to link the tested 46 strains of *Clostridia* to the upregulation of IgE by the mechanism of induction of Foxp3⁺ Tregs.

(158) Despite this complete absence of data, the OD decided that the extremely broad claim scope was plausible. This is inconsistent with the view of the Board of Appeal in D67. The OD's decision here is clearly wrong.

7.3 There is no teaching of how to determine proliferation or accumulation of regulatory T cells in a patient

(159) The claims require that the bacteria from the genus *Clostridium* induces **proliferation or accumulation** of Foxp3⁺ regulatory T cells in the individual. The patent does not provide the skilled person with any guidance how this is to be determined. The claims also require that a treatment effect can be achieved by inducing the proliferation of Foxp3⁺ Tregs or by inducing the accumulation of Foxp3⁺ Tregs.

(160) The Guidelines F-IV, 4.11 set out that:

*“What is decisive for establishing insufficiency within the meaning of Art. 83 is whether the parameter, in the specific case, is so ill-defined that **the skilled person is not able, on the basis of the disclosure as a whole and using his common general knowledge, to identify (without undue burden) the technical measures necessary to solve the problem underlying the application at issue.**”*

(161) The Boards of Appeal have come to similar conclusion in cases where the skilled person does not know when she is working within the forbidden area of the claims (e.g. T256/87).

(162) For the *accumulation* of Tregs, there is no guidance regarding the cut-off at which accumulation is deemed to have occurred. Furthermore, the data provided in the patent provides a percentage of FoxP3-positive cells in the CD4 population. This does not mean an *accumulation* of cells, because the total number of cells in the population could change or decrease. If the skilled person detects an increase in the percentage of FoxP3-positive cells but decreased total CD4 count, does this fulfil the requirement for accumulation, or not? The patent does not provide enough technical guidance in this regard, to determine this essential feature of the claim.

(163) For *proliferation* of Foxp3⁺ Tregs, there is no method described how to determine, in an individual, that the bacterial combination induced proliferation. An increased number of Treg cells

does not necessarily mean increased proliferation, because this could result from reduced destruction of cells, or a change in turnover without affecting proliferation.

(164) These points are **critical** because it was known in the art that bacteria from the genus *Clostridium*, in the form of faecal matter or chloroform treated faecal matter, and clostridia from other genera were known for the treatment of autoimmune diseases in the art. If the Patentee attempts to distinguish the claimed subject matter from the prior art on the basis of the feature of the alleged mechanism of action, then the measurement of this mechanism is of vital importance to the skilled person being able to determine whether this key feature of the claims is met.

(165) In section 8.3.5 of the decision, the OD wrongly characterizes these arguments as relating to clarity, showing a fundamental lack of understanding of the importance of this parameter to determining whether induction or proliferation of Foxp3+ Tregs has actually taken place because the parameter is not in common usage in the art, nor is it defined in the patent.

6.4 Summary of Article 83 EPC

(166) The OD erred in its decision when finding that the claims of the patent met the requirements of Art 83 EPC. The patent fails under Article 83 EPC because the claimed invention is **not made plausible** by the application as filed, the claims are excessively broad and there is **an undue burden** on the skilled person to work the claim across the whole range claimed.

(167) The data in the patent are a mechanistic analysis of the interaction between colonic induced-Tregs and a large combination of 46 unidentified, spore-forming *Clostridium* strains. The only evidence of a potential therapeutic utility is shown for colitis using a 46 strain combination. The use of the 46 strain combination to treat other disorders is speculative.

(168) Furthermore, the data are only supportive of physiological effects being provided by a 46 *Clostridium* strain combination. The exact nature of each strain in the 46-strain combination is not disclosed. There is no evidence that any single *Clostridium* strain, or any other combination of *Clostridium* strains, provide a therapeutic effect in a patient. The OD erred when ignoring the overwhelming body of evidence that single strains of *Clostridium* and the majority of combinations of strains of *Clostridium* do not achieve the induction of Foxp3+ Tregs, let alone any clinical effect.

(169) Therefore, the claims are far broader than the technical disclosure. The claimed medical uses are not plausible across their scope. If there is an invention somewhere within the very limited data, then the claims must be limited to reflect that alleged invention, in which area the skilled person can work the invention without an undue burden.

(170) The OD also erred in ignoring the content of D67, characterising it as unconvincing, very general and preliminary.

7. Priority

(171) The patent claims two priorities: JP2010-129134 (4th June 2010) and PCT/JP2010/071746 (3rd December 2010). The claims are not entitled to either priority date because the priority

documents do not describe the same invention as is now claimed. The OD was incorrect to decide that any of the subject matter of the claims was described and enabled by the disclosure of the priority documents.

(172) The OD acknowledged, to some extent, that the claims as granted were not entitled to the first priority date. However, the OD wrongly concluded that the claims were partially entitled to priority, insofar as the proliferation or accumulation of Tregs took place in the colon and the disease to be treated was an autoimmune disease. However, this decision did not take into account other, significant failings of the disclosure of the first priority application which provides no technical support for the subject matter of the claims whatsoever. For the claims to be sufficiently supported by the technical content of P1, the data therein must have provided clear evidence that a clinical effect in the treatment or prevention of autoimmune diseases. As already explained herein, even the much more extensive data in the patent do not sufficiently support these claims. The OD acknowledged in its decision that there is no data to support the treatment or prevention of any disorder, even in the patent let alone in P1. It is simply not plausible that the very limited data in P1 could sufficiently enable any medical use claim.

(173) Another important point relates to the OD's definition of the term "genus" Clostridium as being interpreted in a taxonomic sense. Paragraph 43 of D67 shows that the Board of Appeal rejected the argument that the data in the patent enables conclusions to be drawn regarding any specific bacteria present within the 46-strain composition:

43. At present, the patent proprietor's counter-arguments (see reply, paragraphs 131 to 158) are not found to be persuasive. The data in the application relied on by the patent proprietor do not show that bacteria of the genus Clostridium of the two clusters IV and XIVa in combination are able to induce Foxp3-positive regulatory T cells to a therapeutically beneficial level and any effects disclosed in the application for the composition of 46 strains cannot be attributed to bacteria of the genus Clostridium of the two relevant clusters, IV and XIV, alone.

(174) The claims, however, require that essentially any bacteria from the genus Clostridium, alone or in combination, will provide the claimed therapeutic effect. In the case of the priority documents, this effect must be supported by the data in the priority documents themselves. Thus, the priority documents must demonstrate that it is bacteria from the taxonomic genus Clostridium that induces FoxP3+ Tregs.

(175) It is clear from the minutes that at the oral proceedings, this point on interpretation and the role of bacteria from the taxonomic genus Clostridium was not discussed when considering sufficiency because the OD decided on priority before looking at the meaning of the claims. In particular, in section 6.1 of the decision the OD referred to parts of the patent that are not present

in P1 or P2, for example Fig 49, to justify this interpretation of the term “genus”. The same figure is essential to the position taken by the OD in section 8.3.1 – Figure 49 is allegedly critical to understanding that the 46 strains contain bacteria from the taxonomic genus Clostridium. These parts are missing from P1 and P2, and therefore the justification used by the OD regarding the meaning of the term “genus” Clostridium cannot hold for the meaning of the term in P1 and P2.

(176) In fact, P1 uses a completely different definition of “genus” Clostridium to that taken by the OD. In paragraph [0017], P1 defines this term as follows:

“There are no particular restrictions on the ‘bacteria belonging to the genus Clostridium’ that are used as an active ingredient in a composition of the present invention as long as the bacteria have an action inducing proliferation or accumulation of regulatory T cells.”

(177) It is evident, therefore, that the definition of this critical term changed between the filing of P1 and the filing of the patent, if the OD has indeed interpreted the term correctly. Furthermore, the interpretation taken by the OD that the genus Clostridium is meant in a taxonomic sense, and that the 46 strains of Clostridium used in the examples are taxonomically of the genus Clostridium relies on the phylogenetic analysis shown in Figure 49. Figure 49 and any discussion of phylogenetic analysis or 16S rRNA is missing from P1.

(178) JP2010-129134 (“P1”) is a very different – and shorter – disclosure than the application as filed. In particular, P1 contains only Examples equivalent to 1 to 4, 7, 9, 11, 12, 13 and 14 from the application as filed. Therefore, P1 does not make it plausible that essentially all bacteria from the genus clostridium would lead to the treatment of autoimmune diseases and allergic diseases by the induction of Foxp3-positive regulatory T cells. The failings described above under Article 83 EPC are therefore even greater for the lesser technical disclosure of P1.

(179) PCT/JP2010/071746 (“P2”) also fails to disclose all features of the claimed invention. In particular, Examples 17 and 18 and corresponding Figures 49 to 53 from the application as filed are not present in P2. The description and SEQ ID NOs. relating to the 16S sequencing of strains used to arrive at Figure 49, in Example 7 of the application as filed, are also missing from P2.

(180) Thus it would appear that data the OD considered to be essential to showing that bacteria from the taxonomic genus Clostridium can induce FoxP3+ Tregs is not present in P1 or in P2. Following the OD’s arguments, the priority documents cannot provide an enabling disclosure of the invention that is now encompassed by the claims of the patent.

(181) Furthermore, Examples 17 and 18 are the only Examples that provide any information at all on strains other than the complete 46-strain combination. Even Examples 17 and 18 do not show that individual strains or combinations of strains are able to induce regulatory T cell proliferation or accumulation to a therapeutically beneficial level, in the absence of the other strains from the 46-strain combination. But the absence of these Examples from P2 makes that

disclosure even more deficient with regard to the present claim that any bacteria of the genus clostridium can induce FoxP3+ Tregs and suppress immunity to a therapeutically-effective level and so treat or prevent any autoimmune disease. Accordingly, P2 does not show that individual strains or combinations of strains are able to induce regulatory T cell proliferation or accumulation to a therapeutically beneficial level.

(182) The lack of Figure 49 and the accompanying description of its creation (added to Example 7 of the application as filed) also means that there is even less information in P2 than in the application as filed, regarding the content of the 46-strain combination of Clostridium spp. used in the Examples. Therefore, P2 does not enable the skilled person to repeat Example 7 because there is no way to know whether the same 46-strain cluster has been provided.

(183) Any claim that is entitled to priority must be directly and unambiguously disclosed, and enabled, by the respective priority document. Both P1 and P2 are lacking in the regard, and the claims are not entitled to either priority date.

(184) In addition to the severe issues of enablement, all of the added matter objections discussed above under Articles 76(1) and 123(2) EPC also apply to both priority documents.

(185) Therefore, the relevant date for the assessment of the prior art, is the filing date of 3 June 2011. The OD was incorrect to consider that P1 gave rise to a partial priority for some of the subject matter of the claims, and was also incorrect to consider that P2 provides an enabling disclosure of the claimed invention.

8. Lack of Novelty

(186) There are three classes of novelty-destroying disclosure. First, there are the inventors' own disclosures during the priority year (D10, D11 and D18). Second, there is disclosure of the use of donor faeces to treat gastrointestinal autoimmune diseases in patients, wherein the donor faeces will inevitably contain bacteria from the genus Clostridium (D14). Third, there are disclosures of bacterial combinations comprising Clostridia for the treatment of inflammatory bowel disease (IBD) in human patients and in animal models (D2, D12 and D13).

(187) The OD's decision on novelty is flawed for a number of key reasons – the OD decided wrongly on entitlement to priority and thus failed to consider intervening publications; the OD decided incorrectly that the claims represented a new clinical situation; and finally by interpreting the term “genus Clostridium” in a strict taxonomic sense when considering the prior art but not then applying that consistently across all other grounds and particularly sufficiency.

8.1 The inventors' own earlier disclosures

(188) The content of these disclosures is the same information as in the patent, and indeed even goes beyond what was included in the patent.

8.1.1 D10 - Atarashi et al, 2010

(189) D10 is a publication by some of the inventors in the priority year of a mouse colitis model being treated with a combination of bacteria from the genus *Clostridium* that induce Tregs, so is a specific disclosure that deprives claim 1 of novelty. D10 published after the claimed priority dates but before the filing date of the Patent. It is full prior art for all subject matter that is not entitled to either of the claimed priority dates.

(190) D10 contains many of the experiments in the patent. However, it is noteworthy that, as noted above, D10 contains a number of key experiments relating to bacteria from the genus *Clostridium* that are **not present in the patent**. For example, D10 states at page 5, paragraph 2, line 4, that:

“...*Clostridium* spp. belonging to clusters IV and XIVa are outstanding inducers of T_{regs} in the colon.”

(191) Based on this additional technical content not present in the patent, the abstract of D10 provides a clear novelty-destroying disclosure for at least claims 1, 2 and 3 (underlining added):

CD4⁺ T regulatory cells (T_{regs}), which express the Foxp3 transcription factor, play a critical role in the maintenance of immune homeostasis. Here, we show that in mice, T_{regs} were most abundant in the colonic mucosa. The spore-forming component of indigenous intestinal microbiota, particularly clusters IV and XIVa of the genus *Clostridium*, promoted T_{reg} cell accumulation. Colonization of mice by a defined mix of *Clostridium* strains provided an environment rich in transforming growth factor- β and affected Foxp3⁺ T_{reg} number and function in the colon. Oral inoculation of *Clostridium* during the early life of conventionally reared mice resulted in resistance to colitis and systemic immunoglobulin E responses in adult mice, suggesting a new therapeutic approach to autoimmunity and allergy.

8.1.2 D11 – Honda et al 2011

(192) D11 is another publication by some of the inventors in the priority year, this time a conference abstract published in April 2011. It is full prior art for all subject matter that is not entitled to either of the claimed priority dates.

(193) D11 recites (lines 4-5 of the English-language part) that:

*“...the spore-forming and gram positive component *Clostridium* spp. belonging to clusters IV and XIVa are outstanding inducers of Tregs in the colon.”*

(194) D11 goes on to disclose that colonisation of mice by a mix of 46 strains of *Clostridium* spp. provided an environment rich in TGF- β and affected IL10⁺ Foxp3⁺ Treg number and function in the colon. These findings are said to suggest that *Clostridium* increase the number of Tregs and induce a shift in the composition of Tregs, in the colonic lamina propria, which may suggest potential therapeutic options for treating human autoimmune diseases and allergies.

(195) This is a disclosure of all features of at least claims 1, 2 and 4.

7.1.3 D18 - Atarashi et al – 25 August 2010

(196) D18 is a poster presented by some of the present inventors at the 14th International Congress of Immunology held on August 22-27 2010 in Kobe, Japan. In an IDS dated 28 November 2017 on the related US application US 15/487,553 the Patentee filed evidence of the date of publication of D18 on 25 August 2010, i.e. **before the second priority date**. The IDS is enclosed as D18b.

(197) The abstract for the poster is cited as D19. D19a confirms that the abstract was published on 1 August 2010. D19b is an email exchange with the conference organiser, confirming that D19 published on 1 August 2010 and that the corresponding Poster 064-03 (D18) was presented at the conference.

(198) The discussion herein focuses on the poster, D18. The abstract, D19, contains the same key technical disclosure.

(199) D18 describes the regulation of colonic regulatory T cells by Clostridium species. This uses the same DSS model of colitis that is used in Example 15 of the patent. The abstract of D18 discloses that (emphasis added):

*“**CD4+ T regulatory (Treg) cells, expressing the Foxp3 transcription factor, play a critical role in the maintenance of immune homeostasis. Here we show that this subgroup of specialized T cells is most abundant at colonic mucosa, and this abundance is achieved by the presence of spore forming component of indigenous intestinal microbiota – particularly the genus Clostridium belonging to clusters XIVa and IV....***

*Oral **inoculation of Clostridium spp.** during early life of conventionally reared mice results in Clostridium –abundant adult mice, which **exhibit resistance to colitis model.**”*

(200) Figure 5 of D18 provides experimental evidence that DSS-induced colitis in mice is alleviated by Clostridium bacteria. Figure 5B provides evidence that the number of FoxP3+ Treg cells is increased by Clostridium spp. inoculation.

(201) This is a direct and unambiguous disclosure that bacteria of the genus Clostridium prevent the autoimmune disease colitis by maintaining immune homeostasis through achieving abundance of Foxp3+ Tregs. Therefore, D18 anticipates at least claims 1, 2 and 3.

8.2 Use of donor faeces to treat gastrointestinal autoimmune diseases in patients

(202) In section 11.4 of the decision, the OD reasoned that the claims as granted represented a new clinical situation. At the Oral Proceedings, the OD was unable or unwilling to provide a definition of this new clinical situation.

(203) In section 11.4.5 of its decision, the OD lists a number of new clinical situations that rely on features that are not present in the claims. For example, the OD refers to avoiding the risks or

side effects of FMT as a possible new clinical situation. This, despite acknowledging that **the claims encompass using FMT**, and therefore do not actually achieve the stated objective of avoiding any risks associated therewith.

(204) No new clinical situation could be based on the alleged ability to exclude pathogenic or deleterious strains of bacteria from the composition – such strains are not excluded from the claimed composition. Furthermore, the comments of the OD in section 11.4.6 referring to subsets of bacteria prepared to high laboratory standards is not relevant because this is not what is specified in the present, open-ended claims, which have no limits on the purity of the composition.

(205) Another potential new clinical situation given in in section 11.4.5 of the OD's decision is the specific selection of patient subgroups. However, as discussed below, there is no new, non-overlapping group of patients that can be treated with the compositions of the claims – not least because the compositions for use according to the claims encompass FMT and are open-ended. The new clinical situation is certainly not a new patient population, as no such population is specified in the claims. It is furthermore not the treatment of a new disorder or any subset of the disorders that are treated in the art, as there is complete overlap in the definition of the disorder to be treated.

(206) The compositions for use according to the claims simply need to comprise bacteria of the genus *Clostridium*, which bacteria can induce proliferation or accumulation of Foxp3+ Tregs.

(207) Another alleged new clinical situation was the possibility to treat a wider range of diseases. However, the specific disclosure in the art of treating the autoimmune disease IBD takes away the novelty of the treatment of autoimmune disease generally.

(208) Put simply, there is no new clinical situation that is aligned with the wording of the claims. In section 11.4.6 of the decision, the OD refers to a composition for use according to the claims as having been prepared to a “high laboratory standard”. There is no such limitation in the claims. The OD also referred to the bacteria being “concentrated” and provided in a “small dose”. The claim contains no limitations as to purity or concentration and no dosage limitation. The OD incorrectly read into the claims limitations that are not there.

(209) The skilled person could only arguably be in a position to act differently and adapt a therapeutic approach to avoid risks or side effects known in the prior art if the claimed composition did not encompass the prior art compositions. To the extent that the claimed composition covers FMT (which appears to have been agreed by the OD), there cannot be a new clinical situation, and certainly not one based on unsubstantiated advantages of a composition “consisting of” particular, unspecified strains of *Clostridia* which appears to be the reasoning that underlies the reasoning from the OD.

(210) According to the established case law of the Boards of Appeal, the use of the same compound in the treatment of the same disease for a particular group of subjects can only constitute a novel therapeutic application if it is carried out on a new group of subjects which is

distinguished from the former by its physiological or pathological status. These groups cannot be overlapping. The claims are not appropriately limited to any new patient population. In T2232/17 the Board confirmed that the patent must disclose the patient sub-group and also disclose data on the treatment of that subgroup to demonstrate a special therapeutic or pharmacological effect that could be the basis for establishing a new patient group. There are no such data in the opposed patent.

(211) Fundamentally, the arguments presented by the patentee and accepted by the OD do not align with the open-ended, exceptionally broad nature of the claim. In summary, the claims fail to exclude compositions such as FMT, so there is no new clinical situation, nor is there any new patient population that is associated with the claims.

7.2.1 Borody (D14) discloses the use of bacteria from the genus *Clostridium* for the treatment of colitis

(212) D14 discloses the use of faecal material transfer (FMT) for the treatment of ulcerative colitis. Ulcerative colitis is an autoimmune disease and is a subset of IBD.

(213) D14 reports the clinical, colonoscopic and histological effects of human probiotic infusion (HPI) in 6 patients with ulcerative colitis (UC).

(214) Patients nominated a suitable donor for HPI. Donors were required to be healthy adults with normal bowel function and no other ailments, having taken no antibiotics for at least 6 weeks. Donor faecal specimens were screened for common pathogens.

(215) Prior to HPI, patients received antibiotics intended for the suppression of *Clostridium* followed by a single orthostatic lavage with polyethylene glycol-based oral solution. Donor faeces was diluted in normal saline and administered to the patient via enema within 10 minutes of preparation. Patients were encouraged to retain the enema for as long as possible (at least 6–8 h). This process was repeated daily for 5 days.

(216) The inevitable presence of bacteria from the genus *Clostridium* in healthy human faeces is confirmed by the following prior art documents:

- a. D16 reports the comparison of gut microbiota from three healthy subjects by the use of a sequence analysis of 16S rDNA libraries and a culture-based method. Although there was considerable variability between subjects, the 16S rDNA libraries and cultivated bacteria of all three samples included, inter alia *Clostridium* rRNA clusters IV and XIVa (see Table 1 and Figures 1 and 2).
- b. D17 reports the investigation of the population structure of the predominant phylogenetic groups within the human adult faecal microbiota. Application of six 16S rRNA-targeted oligonucleotide probes to faecal samples from 27 human adults showed additivity of 70% of the total 16S rRNA detected by the bacterial domain probe. The *Bacteroides* group-specific probe accounted for 37% ± 16% of the total rRNA, while the enteric group probe accounted for less than 1%.

Clostridium leptum (i.e. cluster IV) and *Clostridium coccooides* (i.e. cluster XIVa) group-specific probes accounted for 16% ± 7% and 14% ± 6%, respectively, while *Bifidobacterium* and *Lactobacillus* groups made up less than 2% (see Abstract and Table 3 wherein all of the individuals measured have detectable levels of the two clusters).

(217) Therefore, the faecal compositions administered in D14 inevitably comprise bacteria belonging to the genus *Clostridium*. These compositions are pharmaceutical compositions because the donor faeces was formulated in saline and administered to the patient via enema in a clinical setting. The “comprising” language in the claims therefore encompasses FMT as described by D14.

(218) Furthermore, the treatment regimen in D14 resulted in improvement of symptoms of UC 1 week post-HPI and complete reversal of symptoms in all patients by 4 months post-HPI. At 1 to 13 years post-HPI and without any UC medication, there was no clinical, colonoscopic, or histologic evidence of UC in any patient (see Abstract). The authors conclude that colonic infusion of donor human intestinal flora can reverse UC in selected patients.

(219) Thus, D14 discloses the use of a composition comprises bacteria belonging to the genus *Clostridium* in a method of treating an autoimmune disease (UC) in an individual.

(220) D14 does not mention proliferation or accumulation of transcription factor Foxp3-positive regulatory T cells. D14 does refer to mucosal production of IL-10 on page 46, right hand column, second full paragraph. In discussing the data in the patent, the OD concluded that the skilled person would regard IL-10 production in the colon as a proxy for induction of Foxp3+ Tregs, as IL-10 was known to be a downstream effector of Foxp3+ Treg control of the immune response. If this reasoning is followed consistently, then the skilled person would understand that FMT causes an upregulation of Foxp3+ Tregs. This is confirmed in paragraph 4 of the background section of the patent, which states:

“Moreover, it has been known that the Foxp3-expressing cells are present in a large number especially in the colon, and only Treg cells present locally in the colon constantly expresses IL-10, which is an immunosuppressive cytokine, at a high level (Non-Patent Document 17)”

(221) However, in order to be novelty destroying, it is not necessary to show that the mechanism of action was disclosed, explicitly or implicitly. This mechanism is simply additional information that cannot confer novelty on the known therapy. It does not, for example, provide a new patient subgroup or other clinically-relevant limitation. This feature therefore represents a mere explanation of an underlying mechanism that still cannot confer novelty on the known therapy.

(222) In T233/96 the Board of Appeal held that if the use of a compound was known in the treatment or diagnosis of a disease of a particular group of subjects, the treatment or diagnosis of the same disease with the same compound could nevertheless represent a novel therapeutic

or diagnostic application, provided that it was carried out on a new group of subjects which was distinguished from the former by its physiological or pathological status (T19/86, T893/90). This did not apply, however, if the group chosen *overlapped with the group previously treated*, or the choice of the novel group was arbitrary which meant that no functional relationship existed between the particular physiological or pathological status of this group of subjects and the therapeutic or pharmacological effect achieved.

(223) The choice of such a novelty-establishing subgroup must not be arbitrary (T1399/04). Furthermore, a new therapeutic application was deemed to be incompletely disclosed if the subject to be treated was not identified; only a disclosure of **both the disease and the subject to be treated** represented a complete technical teaching. In the present case, there is no identification of a new subject or patient group to be treated, nor even any specific disease that can be treated other than colitis.

(224) The patent does not identify any new patient group, and certainly not a non-overlapping group of subjects, that would not be treated by the use of the compositions disclosed in D14 for the treatment of colitis as a model for the autoimmune disease IBD.

(225) Put simply, the claimed composition does not exclude FMT, and therefore cannot lead to a new clinical situation compared to the prior art FMT-based therapy.

(226) In T836/01, the Board considered that the claimed medical use relied upon a **different technical effect** from the prior art disclosure of the same agent for activating cytotoxic T lymphocytes against cancer cells. The Board held that the prior art indirect effect did not anticipate the claimed direct effect on cancer cells. This was because the identification of the new and different effect was clinically relevant. However, the Board emphasised at paragraph 8 of its reasons that identification of a **new property does not automatically establish novelty** (emphasis added):

*"It must be pointed out that a **hitherto unsuspected property of a known molecule/composition does not necessarily translate into a novel use (be it medical or otherwise)** of that molecule/composition, but for an application to be construed as a further use or 'further medical use'/'further therapeutic application', this new technical effect **would have to lead to a truly new industrial/commercial application** (see eg decision G5/83, point 16) arising from eg the opening a new field of application, the healing of a different pathology/clinical situation, the creation of a distinct group or sub-group of subjects (either end-users or patients) or the new use must involve new physical means/measures for its practise."*

(227) Without any new clinical situation that is clearly identified in the disclosure of the patent, any arguments based on the case law relating to new clinical situations or new patient sub-groups must fail.

(228) Therefore, D14 anticipates at least claims 1, 2, 3 and 4.

8.3 Compositions comprising bacteria of the genus *Clostridium* for treating autoimmune disease

8.3.1 D2 discloses the use of *Faecalibacterium prausnitzii* to treat colitis

(229) D2 discloses that a Clostridia cluster IV bacterium (*F. prausnitzii*) is effective in a murine model of colitis and “*is a promising strategy in [Crohn’s Disease] treatment*” (see final sentence of abstract). The patent at paragraph [0008] and D2 both confirm that *F. prausnitzii* is a clostridium, and was the major component of the *C. leptum* group (cluster IV) in human faecal matter.

(230) D2 does not explicitly disclose that *F. prausnitzii* induces proliferation or accumulation of Foxp3-positive regulatory T cells. D2 does, however, disclose that treatment with this particular Clostridium induces the expression of IL-10 in the colon of treated mice on page 16733, in the right hand column, third paragraph,:

“F. prausnitzii and Its Supernatant Induce an Increased Secretion of IL-10 and a Decreased Secretion of TNF- α and IL-12 in TNBS-Induced Colitis in Mice.

*Forty-eight hours after TNBS instillation, colonic proinflammatory TNF- α and IL-12 cytokines and anti-inflammatory IL-10 were quantified by ELISA (SI Materials and Methods and Fig. 5). Compared with the no-colitis control group, TNF- α and IL-12 levels were increased, whereas IL-10 levels were barely modified. In the two TNBS groups treated with either *F. prausnitzii* or its supernatant, the secretion of TNF- α and IL-12 was significantly lower than in the colitis control group. Interestingly, IL-10 secretion was induced in the colon of mice treated with *F. prausnitzii* or its supernatant.” [emphasis added]*

(231) As stated in the introduction to the patent, the inventors were seeking to identify the mechanism by which IL-10 was induced in the colon. Paragraph [0005] explains that:

“Accordingly, if the mechanism of the induction of Treg cells which produce IL-10 in the colon at a high level is elucidated, immunosuppression can be enhanced, which in turn can be applied to treatment of autoimmune diseases such as inflammatory bowel disease...”

(232) D2 clearly teaches that one mechanism for the induction of IL-10 in the colon is the use of the Clostridial bacteria *F. prausnitzii*. The patent, if it contributes anything, merely elucidates an intervening step in the pathway to induction production of IL-10.

(233) However, the OD, when considering the data in the patent, concluded that in respect of Example 16, IL-10 production was a suitable proxy for Foxp3+ Treg proliferation or accumulation. While this would not appear to be the case outside of the colon, there is more evidence that this was already known in the art to be the case in the colon. As stated in the background section of the patent, in paragraph [0004], it was already known in the art that the large intestine has a high level of IL-10+ Foxp3+ cells. The skilled person would therefore have readily understood that the IL-10 production in D2 was likely derived from Foxp3+ Tregs in the colon.

(234) Furthermore, in D23 the inventors of the patent note at page 2, right hand column, penultimate paragraph that *F. prausnitzii* is “a human Clostridia strain well known for enhancing regulatory T cell functions”, with reference to the FoxP3+ CD4 cell count of Figure 2D. The ability of *F. prausnitzii* to induce FoxP3+ Tregs is also shown in the data in D25 (e.g. Figure 10 FoxP3+ panels), and in the declaration and experimental evidence provided as D26, which confirm that *F. prausnitzii* does indeed have this effect on the accumulation of FoxP3+ Tregs.

(235) D2 therefore discloses all of the features of claims 1, 2 and 3. There cannot be any “new clinical situation” in respect of D2, because the underlying mechanism of action in both cases is the same – IL-10 production in the colon is increased to treat an autoimmune disease.

8.3.2 D12 and D13 each disclose Clostridia for treating IBD in humans

(236) D12 and D13 each discloses the use of Clostridial clusters for the treatment of an autoimmune disease, IBD in human patients. The compositions contain selected, well characterised intestinal bacteria taken from normal humans to replace the patient's intestinal bacteria. The strains that are used include strains from Clostridium cluster IV such as *Fusobacterium (Faecalibacterium) prausnitzii* and *Ruminococcus bromii*, and strains from Clostridium cluster XIVa such as *Eubacterium rectale*, *Ruminococcus obeum* and *Ruminococcus gnavus*. D13 also includes the cluster XIVa strain *Coprococcus eutactus (lachnospiraceae)*.

(237) The bacteria in D12 and D13 are not of the taxonomic designation *Clostridium* spp. but are Clostridia.

(238) In the opposition proceedings in respect of the grandparent patent, the Patentee maintains that the person skilled in the art would not draw a distinction between the terms “genus Clostridium” and “Clostridia”. In its submission of 18 December 2018, the Patentee asserted at paragraph 8 on page 5 that:

“...the application as originally filed and P2 do not employ the phrase “bacteria belonging to the genus Clostridium”, as the opponents allege, in a narrow taxonomic sense that limits the original disclosure to bacteria that include the term “Clostridium” as the genus in their taxonomic name. Rather, the application as originally filed and P2 (hereinafter: the “Original Disclosure”) employs the term in a broad, “non-taxonomic” sense...”

(239) This interpretation is based on an expert declaration by Professor Sorg, which is D21 in these proceedings, which in turn relies on the document numbered as D22 in these proceedings. The Patentee maintained this interpretation in the appeal proceedings on the grandparent patent, as can be seen (for example) in paragraph 49 of their letter of 24 February 2020 in that case.

(240) The Patentee's interpretation of the term “genus Clostridium” was that it should not be interpreted in a narrow taxonomic sense (i.e. Clostridium spp.) but refers to Clostridia more generally (i.e. Clostridial “Clusters”). The Patentee's new “phenetic” interpretation is yet broader again. Therefore, either of the Patentee's definitions would include the Clostridia of D12 and D13, such as *Faecalibacterium prausnitzii*.

(241) D13 describes bacterial replacement therapy, but does not propose a mechanism by which this is effective. The absence of a mechanistic explanation for a clinically-observed effect is not the same as the provision of a different mechanism, so following T836/01 a *different* mechanism is not proposed that might restore novelty of the claim.

(242) D12 discloses bacterial compositions for the treatment of the autoimmune disorder inflammatory bowel disease (IBD) in human patients, wherein the bacterial compositions interact with the immune system to reduce immune stimulation. D3 describes in the abstract that:

*“The new microflora serve to **generate more normal metabolic and immune responses**, remitting thereby the IBD”.*

(243) D12 goes on, at column 1 lines 54 to 59 to describe that:

*“In addition, the new bacteria will also offer different molecular configurations to the immune receptors. With the **absence or change of immune stimulation, the destructive process will stop**, and there will no longer be pathological inflammation of the intestinal wall.”*

(244) Therefore, D12 describes that the Clostridia change the immune stimulation that causes the destructive process to stop. The claimed subject-matter does not provide a *different* mechanism from this, and instead provides additional detail of the **same immune-mediated mechanism**. Therefore, the reasoning in T836/01 relating to the identification of a different mechanism cannot be relied upon to distinguish the claims, which therefore lack novelty over D12.

(245) In T486/01, the Board considered a claim to the use of IGF-1 for use in reducing the loss of particular cells suffered after a CNS insult. The applicant argued that the activity on certain cell types established novelty of the claim:

1. The use of IGF-1 and/or a biologically active analogue of IGF-1 in the manufacture of a medicament for use in reducing the loss of glial cells or non-cholinergic neuronal cells suffered after a CNS insult.

(246) The Board found that this claim **lacked novelty** over a prior art disclosure of the use of IGF-1 for use in treating a CNS insult e.g. Parkinson's disease. The mechanistic requirement that loss of glial cells or non-cholinergic cells is reduced, **did not render the claim novel**. The board stated at Reasons 12 that (emphasis added):

*"In conclusion, the board considers that, even deciding in the appellant's favour that the physiological effects emphasized by the appellant are not known in the state of the art, **these can only be regarded as the discovery of additional items of knowledge about further mechanisms of action underlying the known therapeutic application of IGF-1 in the treatment of CNS insults, but cannot in themselves confer novelty over this known therapeutic application.**"*

(247) That reasoning applies to the facts in the current case. The cited prior art discloses compositions within the scope of the composition definition in claim 1, for the same medical uses. The alleged discovery of additional items of knowledge about further mechanisms of action underlying the known therapeutic application, does not confer novelty.

(248) The physiological effect specified in the claims of the patent is the induction of proliferation of Foxp3+ T cells. However, this is nothing more than an additional item of knowledge about how an existing composition achieved a known effect. There is no evidence that there is a new patient population that can be treated by inducing the proliferation of Foxp3+ T cells that could not be treated by the mechanism proposed in D12, D13 or D14. There is no evidence of the existence of any treatment effect on any disease other than colitis in the patent, let alone a disease that can be treated purely by the induction of Foxp3+ T cells using the claimed composition. There cannot be any new clinical situation arising from the mechanism of action specified in the claims that is based on the disclosure of the patent.

(249) Accordingly, at least claims 1, 2, 3 and 4 lack novelty over each of D12 and D13.

9. Inventive step

(250) The OD erred in its approach to inventive step. In part, this error stems from other errors already explained above. The OD's inconsistent interpretation of the term "genus Clostridium", wherein the term was interpreted narrowly when considering the prior art, led to highly relevant prior art being disregarded. A double standard when assessing the common general knowledge of the skilled person, which was considered to be extensive in discussions of sufficiency but much

more limited when considering inventive step, has also led to inconsistent decisions on these points. Furthermore, the incorrect finding that the claims were entitled to the priority date has a knock on impact on the OD's decision on inventive step.

(251) As explained above in detail when discussing sufficiency, the patent's technical disclosure is very limited and does not provide a technical foundation for the claims. Therefore, the claims are a great deal broader than the technical content of the patent. This creates a problem under inventive step because the claimed invention is **not plausible** across its full scope (e.g. T1329/04).

(252) It must be remembered that the same level of knowledge must be applied to the skilled person when assessing the disclosure content of the patent and that of the prior art (e.g. as summarised in paragraph 24 of the Reasons for the Decision in T1069/08). In finding the claims to be sufficiently described, to the OD considered that the skilled person would have no problem working the claimed invention across the entire claimed scope, based on minimal technical disclosure. If this is the case, then the same expectation must be applied to the prior art.

(253) There is no evidence in the patent that any Clostridium bacteria provides *an improvement* in the treatment of any autoimmune or allergic disease. In fact, the data in Example 17 indicates that using a proportion of the prior art 46-strain combination produces a commensurately **reduced benefit**. So any technical effect relied upon for the 46-strain combination is not shown to be provided by any single strain or other combination of strains. As discussed extensively under sufficiency, there is considerable evidence that the invention does not work at all when only single strains of Clostridia are used alone.

(254) Any extrapolation of effects that would be required for a finding of enablement, would therefore also be made starting from the prior art and so must result in a finding of obviousness. However, the OD erred in applying a different standard when assessing inventive step.

(255) Furthermore, the OD erred when applying the problem and solution approach, did not take into account the common general knowledge of the skilled person, and incorrectly alleged that the Opponents were using hindsight in their analysis. In particular, the OD erred in its consideration of inventive step by taking into account alleged advantages that are not taught or foreshadowed in the patent, and for which there was no evidentiary support. For example, in section 12.2.1 the OD alleged that the advantages considered to give rise to an inventive step were a theoretical possibility only. Furthermore, the alleged technical effects taken into account by the OD were not even linked to any features of the claims.

(256) Despite acknowledging in section 12.2.1 that the claims are not limited to the claimed bacteria of the genus Clostridium, and that the claims therefore encompass FMT, proceeded to decide that the claims involved an inventive step due to an alleged advantage of the claimed composition over the FMT of the prior art. This cannot be correct. Any inventive step must extend across the whole scope of the claim, and therefore a claim that encompasses FMT cannot derive an inventive step from an alleged advantage over that same, known treatment.

(257) In a further error of reasoning, the OD stated that the claims derived an inventive step from the knowledge provided by the patent that particular bacteria of the genus Clostridium are responsible for the induction of Foxp3+ Tregs. However, the claims are not limited in any way to any specific bacteria of the genus Clostridium.

(258) The OD continued by stating that the claimed invention involved an inventive step because it allowed for the selection of the particular bacteria and simultaneous exclusion of other bacteria, resulting in a more specific bacterial composition with less adverse effects. This reasoning is flawed on many levels.

(259) The claimed compositions, as acknowledged by the OD, are worded with open language and therefore are not limited to any selection of particular bacteria and simultaneous exclusion of other bacteria. To fall within the scope of the claims, the composition for use in treating an autoimmune or allergic disease must simply comprise a bacteria from the genus Clostridium, which bacteria is able to induce proliferation or accumulation of Foxp3+ Tregs. This encompasses FMT – precisely the composition the OD reasoned that the present invention was an improvement on. Furthermore, there is no evidence of any reduction in adverse events associated with the claimed composition.

(260) The composition of claim 1 encompasses the prior art FMT of D14, so cannot provide an improvement over that composition. For the OD's reasoning relating to an allegedly improved composition to apply, then the claim must exclude the FMT. It does not.

9.1 Obviousness of claims that are not entitled to priority

(261) As explained above, the claims upheld by the OD are not entitled to either of the priority dates. D10, D11 or D18 are then relevant for the assessment of inventive step. D10 and D11 are available as prior art for claims that are not entitled to either priority date, while D18 is available as prior art for claims that are not entitled to the first priority date.

(262) The inventors published an article in December 2010 (D10) and a related conference Abstract in April 2011 (D11) that reports experiments similar to those presented in the patent *but containing additional data on Clostridium Clusters IV and XIVa*. These additional data include Figure S6 in the journal publication.

(263) D11 conveniently summarises the relevant teaching. This comprises two parts, a Japanese-language part and an English-language part. Taking the English-language section, lines 4 and 5 of the abstract recite clearly that Clostridium species (from Clusters IV and XIVa) induce Tregs in the colon:

erties. Among the indigenous commensal bacteria, the spore-forming and Gram-positive component *Clostridium* spp. belonging to clusters IV and XIVa are outstanding inducers of Tregs in the colon.

(264) The final sentence of the English-abstract links this finding to possible utility in disease:

Identifying the molecular mechanisms underlying the *Clostridium*-host crosstalk will provide invaluable information toward understanding how the gut microbiota regulates immune homeostasis and may suggest potential therapeutic options for treating human autoimmune diseases and allergies.

(265) The Japanese-language part of the abstract provides a more detailed disclosure, and an English-language translation is provided. The conclusion is the same.

(266) As discussed above for novelty, D18 is a poster presentation by some of the inventors. This uses the same colitis model as in Example 15 of the patent and discloses that bacteria of the genus *Clostridium* prevent the autoimmune disease colitis by maintaining immune homeostasis through achieving abundance of Foxp3+ Tregs.

(267) If it is concluded that the patent provides the skilled person with enough technical information to work the claimed invention without an undue burden, then the skilled person would equally arrive at any such claimed subject-matter without inventive effort starting from this very similar disclosure in D10, D11 or D18. So, **to the extent that the patent is enabled, the claims must be obvious.**

9.2 Obviousness of claims that are entitled to priority

(268) The prior art contains a number of highly-relevant disclosures.

(269) For example, it was known from D1 that spore forming bacteria play an important role in intestinal T cell responses in autoimmune disorders. D1 specifically notes the effect of *Clostridium coccoides* and *Clostridium leptum* groups of bacteria on intestinal T cell populations including FoxP3+ expression, and observes that Clostridia-related bacterial species enriched in the nonculturable fraction of the bacterial flora are necessary to promote efficient maturation of the intestinal adaptive T cell responses.

(270) It was also known, from D2, that a Clostridia Cluster IV bacterium (*F. prausnitzii*) is an anti-inflammatory bacteria identified by gut microbiota analysis of Crohn's disease patients, and that this Clostridial bacterium can be used as a treatment for Crohn's disease by inducing IL-10 production in the colon. D24 also describes the interaction between host gut microbiota and gut immune cells, proposing that some forms of IBD may be treated by redressing microbiological imbalances and noting that Clostridium clusters IV and XIVa are notably depleted in IBD patients.

(271) The use of compositions comprising Clostridia to treat autoimmune diseases of the gut (IBD) is well-known, for example from D7, D12 and D13. D14 describes the use of faecal matter transfer to treat ulcerative colitis, and it is well known (e.g. D15, D16 and D17) that faecal matter contains a high proportion of Clostridium bacteria.

(272) D8 describes that spore-forming clostridia isolated from faeces of limited flora mice have a positive effect on caecal size when administered to germ-free mice. D9 describes in general terms that spores are resistant to stomach acid compared to the corresponding vegetative cells.

(273) The modulation of regulatory T cells for therapeutic purposes was known, as discussed in D4 to D6. The use of bacteria (*L. reuteri*) to induce FoxP3+ Regulatory T cells and protect against an allergic airway response when administered locally to the airway, was even known from D3.

(274) Accordingly, there was a rich seam of knowledge regarding the treatment of IBD using Clostridium, and of the involvement of microbiota in modulating local host T cell responses, including FoxP3+ Tregs, in IBD.

(275) The closest prior art is the document directed to the same purpose and with the most structural features in common as the invention (Case Law of the Boards of Appeal, I.D.3.1, 167):

“The boards have repeatedly pointed out that the closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications”

(276) As established in T1742/12, a piece of prior art on the basis of which the claimed invention is considered non-obvious cannot be "closer" than a document on the basis of which the claimed invention appears obvious, because it is evident in this situation that the former does not represent the most promising springboard from which to arrive at the invention (see T 824/05, Reasons 6.2).

(277) With this in mind, each of D14, D1 and D2 are suitable candidates as closest prior art.

9.2.1 D2 as closest prior art

(278) D2 is a suitable choice of closest prior art. D2 demonstrated that a Clostridia cluster IV bacterium (*F. prausnitzii*) is effective in a murine model of colitis and “*is a promising strategy in [Crohn’s Disease] treatment*” (see final sentence of abstract).

(279) D2 does not explicitly disclose that *F. prausnitzii* induces proliferation or accumulation of Foxp3-positive regulatory T cells. D2 does, however, disclose that *F. prausnitzii* induces an increase in the level of IL-10 in the colon of treated mice. This is the same aim that the inventors were trying to achieve – as outlined in paragraph [0005] of the background to the patent the inventors sought to understand the mechanism by which IL-10 could be induced in the colon. D2 was therefore directed to the same purpose as the invention, inducing IL-10 to enhance immunosuppression.

(280) It was known in the art, as acknowledged in the background section of the patent and explained above, that IL-10 was known to be produced in the colon by Foxp3+ Tregs. The OD, when considering sufficiency, considered that this knowledge was enough for the skilled person to consider that IL-10 is a suitable proxy marker for Foxp3+ Tregs. This was particularly true when considering the colon, where the link between Foxp3+ Tregs and IL-10 expression was part of the common general knowledge of the skilled person.

(281) Furthermore, in D23 the inventors of the patent note at page 2, right hand column, penultimate paragraph that *F. prausnitzii* is “a human Clostridia strain well known for enhancing regulatory T cell functions”, with reference to the FoxP3+ CD4 cell count of Figure 2D. The ability of *F. prausnitzii* to induce FoxP3+ Tregs is also shown in the data in D25 (e.g. Figure 10 FoxP3+ panels), and in the declaration and experimental evidence provided as D26, which confirm that *F. prausnitzii* does indeed have this effect on the accumulation of FoxP3+ Tregs. Thus, it has subsequently been shown that IL-10 is indeed a suitable proxy for Foxp3+ Tregs in this particular situation.

(282) In the absence of a technical effect associated with the difference from the closest prior art, the objective technical problem starting from D2 may be formulated as the provision of an **alternative composition** comprising a further bacteria from the genus Clostridium for the treatment of IBD.

(283) D1 already teaches that spore-forming bacteria play an important role in intestinal T cell responses in autoimmune disorders. D1 specifically notes the effect of *Clostridium coccoides* and *Clostridium leptum* groups of bacteria on intestinal T cell populations including FoxP3+ expression, and observes that Clostridia-related bacterial species enriched in the nonculturable fraction of the bacterial flora are necessary to promote efficient maturation of the intestinal adaptive T cell responses.

(284) Therefore, the skilled person starting from D2 would have turned to D1 and arrived at the alternative of the claimed invention without an inventive step.

(285) The claimed alternative is also obvious in the light of the extensive prior art disclosures relating to the use of compositions comprising clostridia for the treatment of autoimmune disorders. For example, D14 describes the use of compositions comprising bacteria from the genus Clostridium for treating an autoimmune disease. The skilled person would therefore have been motivated to try replace the Clostridia cluster IV bacterium *F. prausnitzii* used in the closest prior art with a composition comprising other bacteria, specifically from the taxonomic genus Clostridium, with a reasonable expectation of success in treating IBD.

(286) The 46 strain combination of bacteria from the genus Clostridium used in the examples in the opposed patent was well-known in the art (D8, D15). It was furthermore known in the art that decreases in bacteria from the genus Clostridium, including from clusters IV and XIVa, have been reproducibly reported in the gut of IBD patients (e.g. D24) and are thus probiotic candidates for the treatment of IBD.

(287) Even without a specific prompting, the claims do not involve an inventive step. D2 relates to the use of one strain of bacteria from Clostridium cluster IV. The claims do not relate to any specific selection of an alternative strain of Clostridium, but refer to all bacteria of the genus Clostridium in general. Choosing a Clostridium spp. rather than *F. prausnitzii* would have been an obvious choice, as the majority of Clostridium bacteria are in the strict taxonomic genus Clostridium.

(288) Therefore, the claimed invention is obvious starting from D2 as closest prior art.

8.2.2 D14 as closest prior art

(289) D14 relates to Faecal Matter Transfer, and discloses a pharmaceutical composition comprising bacteria of the genus *Clostridium* diluted in saline and administered to a patient suffering from ulcerative colitis. As explained above, no new clinical situation is identified in the patent.

(290) The claim is directed to a composition that comprises bacteria of the genus *Clostridium*. This claimed subject-matter does not provide any advantage over the *Clostridium*-containing FMT formulation of D14.

(291) For example, there is no exclusion from the claimed composition of any potentially deleterious bacteria, nor any mention in the patent of which bacteria might be deleterious and therefore necessary to exclude from the composition. In any event, the FMT pharmaceutical composition of D14 screened the donor faeces for common pathogens. By the very nature of the open wording of the claim, the composition includes faecal material such as that used for FMT.

(292) Furthermore, the claim is not limited to any specific dose of bacteria, nor does the patent provide any evidence that any specific selection of bacteria can result in the use of a reduced dose. The OD's justification of an inventive step therefore rests purely on unsubstantiated suppositions and does not relate to the features of the claims.

(293) There is no evidence in the patent that the claimed composition provides any unexpected effect or improvement in the induction of T regs above and beyond that which would be achieved by, for example, full faecal material transfer. In fact, the data in Example 17 of the patent indicates that using a proportion of the larger prior art combination produces a commensurately **reduced benefit**.

*The alleged effects are not attributable to any and all bacteria from the genus *Clostridium**

(294) As already explained in relation to sufficiency, the evidence provided in the declaration of Dr San Mateo (D20) demonstrates that the effects on colonic Tregs allegedly shown the examples in the patent cannot be attributed to any and all bacteria from the genus *Clostridia*. D23 further shows that the majority of single strains of *Clostridium* alone cannot induce proliferation or accumulation of Foxp3+ T regs.

(295) It is therefore clear that most of the bacteria of the genus *Clostridia* that have been tested by the patentee are **not** able to induce T regs.

(296) The patent provides no evidence of an improved effect over the disclosure of D14, which also provides a treatment effect in IBD using a composition comprising bacteria from the genus *Clostridium*.

(297) The only feature that could be seen as a difference over D14 is the mechanism of action. This mechanism is not linked to any technical effect. As established in T1118/12, a second medical use claim where novelty is established on a patient subgroup that provides no surprising effect or other technical advantage over the prior art, will be rejected for lack of inventive step. Any alleged surprising effect must be supported by data showing an advantage relating to the new patient subgroup or clinical situation. There are no such data in the current case.

(298) An *improved* composition for the treatment of autoimmune or allergic diseases is therefore not demonstrated by the technical disclosure of the patent. Therefore, the problem starting from D14 must be formulated as the provision of an alternative method of treating IBD using a composition comprising bacteria of the genus Clostridia.

(299) The alternative used in the patent, i.e. the 46 strain composition, is obvious as it is already well-known from D8 and D15.

(300) Therefore, the provision of an arbitrary combination of known Clostridial strains from a known mixture of Clostridial strains would have been obvious to the skilled person starting from the closest prior art.

9.2.3 D1 as closest prior art

(301) D1 could be selected as the closest prior art because its disclosure is at least partly directed to the identification of intestinal commensal bacteria which induce the proliferation of regulatory T cells. For instance, in the “Introduction”, D1 states that “*Deciphering the dialog between the microbiota and the host immune system should facilitate an understanding of how bacteria and their hosts coevolved to maintain mutually beneficial relationships*”.

(302) Using gnotobiotic mouse models, the authors of D1 investigated the impact of the microbiota on host gut responses and found that only a restricted number of microbiota appeared to be involved in stimulating steady-state host gut responses.

(303) The gnotobiotic mouse models used were as follows:

“Conventional” (Cv) mice were normal healthy adult mice.

“Germ-free” (GF) mice were bred at the same facility in plastic isolators.

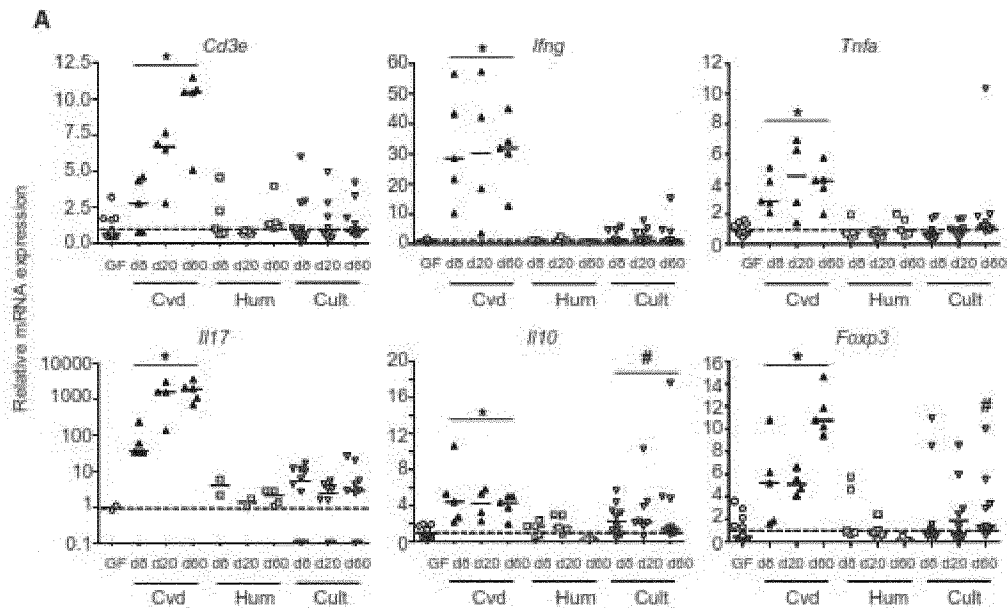
“Conventionalized” (Cvd) mice were created by administration of fresh faeces from Cv mice to GF mice.

“Human” (Hum) mice were created by administration of fresh faeces from a healthy human donor to GF mice.

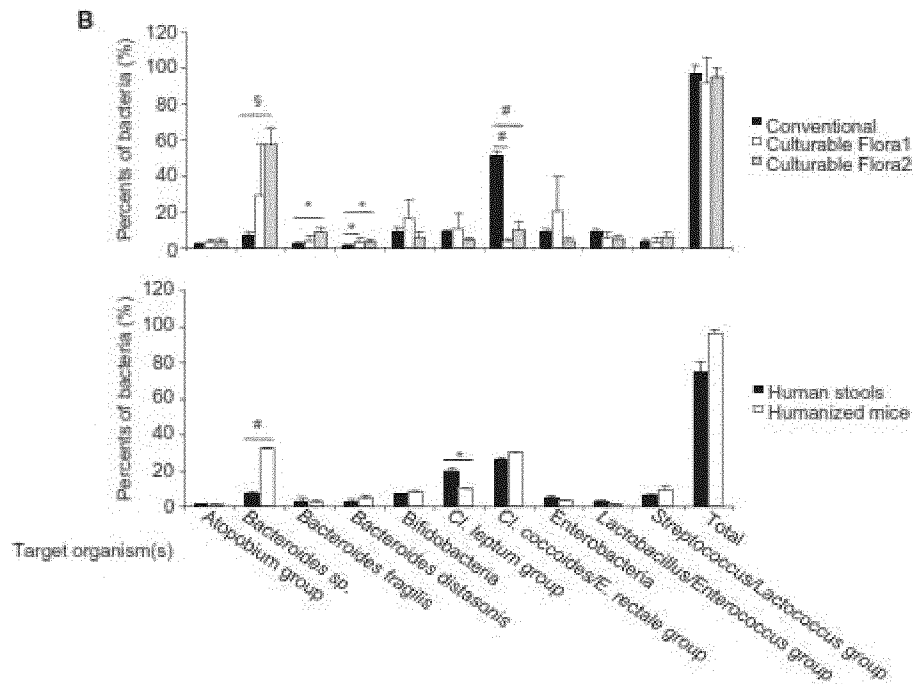
“Cultured” (Cult) mice were created by administration of a fresh mouse faecal homogenate from Cv mice which had been cultured for 4 days at 37°C to GF mice.

“Sporulated” (Spo) mice were created by administration of fresh faeces from Cv mice which had been heated to 70°C for 10 mins to GF mice.

(304) Analysis of changes in intestinal gene expression in Cv and Cvd mice compared to GF mice showed that intestinal colonization resulted in the combined induction of proinflammatory and regulatory T cells (including Foxp3). In order to try and identify which members of the microbiota are responsible for these changes, the authors then analysed ileal transcriptomic responses for a variety of GF mice monocolonized with a number of bacterial strains but these failed to elicit the same responses as those observed in Cv and Cvd mice (data not reported). In addition, they analysed ileal transcriptomic responses for Cult and Hum mice but again failed to stimulate the transcription of most studied immune genes (see Figure below).

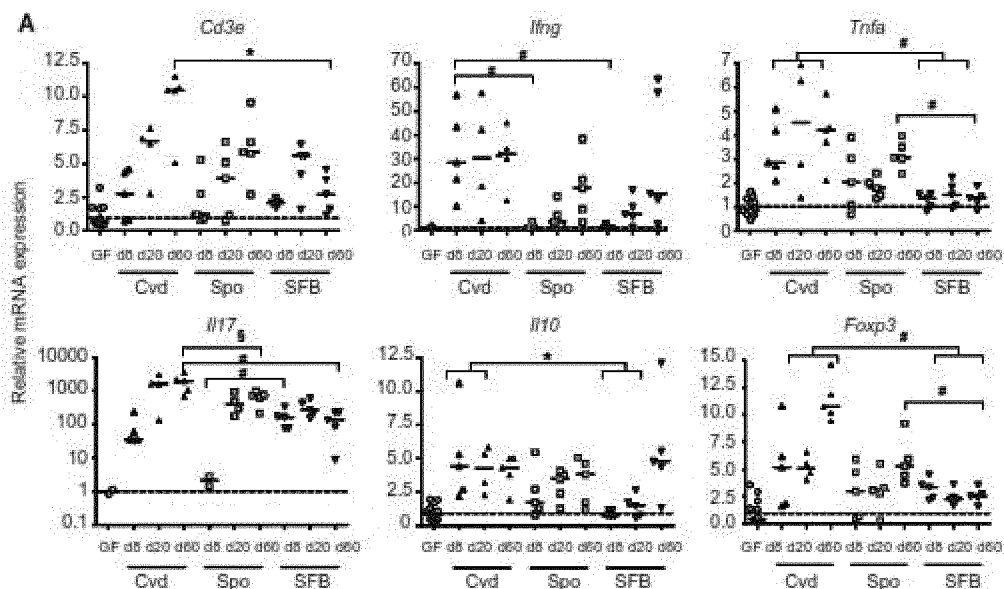


(305) To explain the disparity between the effects of Cv and Cvd mice with Hum and Cult mice, it was postulated that the former contained specific bacterial species capable of stimulating immune activity. Thus, the composition of the microbiota was compared by FISH in the faeces of Cv and Cult mice. Although the flora of Cult mice remained diverse, a notable **reduction in *Clostridium coccoides*** was observed. Similarly, a selective **loss of bacteria from *Clostridium leptum*** was observed when comparing the microbiota in the donor human faeces with that of Hum mice by FISH.



(306) These results led to the hypothesis that **these specific bacteria** were necessary to promote efficient maturation of the intestinal adaptive T cell responses.

(307) To test this hypothesis, Spo mice were analysed and showed a marked increase in ileal mRNA expression for all tested immune markers (including Foxp3) comparable with that observed in Cvd mice (see Figure below).



(308) The authors concluded that these results supported the hypothesis of a key role of one or several spore-forming Clostridium-related species.

(309) Notably, D1 is cited as the inspiration for Example 6 of the patent which is a very similar experiment. The only real difference between the two experiments is that the patent colonised GF mice with faecal bacteria resistant to 3% chloroform (source unspecified) whereas D1 colonised

GF mice with heat-treated microbiota from Cv mice. However, the intention of both treatments was to provide mice with microbiota enriched in spore-forming *Clostridium* bacteria.

(310) To conclude, the closest prior art may be taken as the teaching that administration of faecal bacteria containing only spore-forming *Clostridium* bacteria can induce the proliferation or accumulation of regulatory T cells, in particular Foxp3 cells, to a similar extent as the administration of faecal bacteria from Cv mice (compare results for Spo mice with those for Cvd mice).

The distinguishing feature, technical effect and objective technical problem to be solved

(311) The difference between D1 and the opposed patent would therefore appear to be the use of the bacterial composition to treat the diseases specified in claim 1.

(312) The technical effect of this difference is the provision of a clinical application for the teaching of D1.

(313) As set out above when discussing Article 83 EPC, the patent does not credibly demonstrate that a technical effect is provided by the specific uses.

(314) Based on the lack of a technical effect, the objective technical problem with regard to D1 must be formulated as the provision of **an alternative** use.

The alternative use would have been obvious

(315) An arbitrary alternative is usually non-inventive.

(316) Therefore, if the lack of data in the patent are deemed somehow to enable the skilled person to work the invention without an undue burden, then that skilled person would also have expected the claimed invention to work after having read the prior art.

(317) Again, it is re-stated (i) that if the claims are deemed to be enabled then the assumption of what would be expected to work must be generous, and that generosity must be applied also when considering what the skilled person would do; and (ii) the lack of any evidence of an *improvement* in the patent means that the technical problem is merely an obvious alternative.

(318) D1 itself mentions “*the accumulating evidence of microbial dysbiosis in allergic and inflammatory bowel diseases*” (see Introduction). The patent acknowledges that Foxp3 was already known to play an important role in maintaining immunological homeostasis (see page 3, line 30 to line 46 and associated references). Therefore, it would have been obvious to apply the teaching of D1 in a clinical setting for treating IBD. This is yet further strengthened by D24, which shows that bacteria from the subgroup Lachnospiraceae (which comprises the *Clostridium* clusters IV and XIVa) are significantly depleted in patients with IBD (see Figure 4) and suggests remediation by administration of a probiotic regime.

(319) Therefore, the claimed invention is obvious starting from D1 as closest prior art.

9.3 Conclusion on inventive step

(320) Claims that are not entitled to priority must be obvious over the inventors' own publications of the data in the patent, in the priority year.

(321) Any claim that is entitled to priority is simply an alternative that the skilled person would have tried, with a reasonable expectation of success, based on the teaching of D14, D1 or D2 as the closest prior art and combined with another of those documents, or with D8, D15 or D24.

10. Auxiliary Requests

(322) The patentee filed ARs 1 to 75 on 20 July 2021 and then further ARs 76-79 on 16 August 2023 after receipt of the OD's Preliminary Opinion.

(323) In **AR1**, **AR2**, **AR3** and **AR4**, the only amendments made are to the dependent claims. Therefore, all of the objections to the independent claim in the patent as granted, explained above, still apply.

(324) In **AR3** (and all Auxiliary Requests comprising the amendment of AR3), the use of the term "preferably" is unclear contrary to 84 EPC, because it does not limit the claim. Furthermore, the Patentee asserts that this amendment does not change the substance or subject-matter of the claims, in which case there seems to be no need for the amendment contrary to Rule 80 EPC.

(325) **AR5** recites that the Tregs are induced in the colon. This causes the issues of enablement across the scope of the claims to be even more acute. There is no evidence of plausible link between the induction of Tregs in the colon and the treatment of diseases that are not linked to dysfunction of the colon such as Alzheimer's disease, MS and/or any other autoimmune or allergic disease whose aetiology is unrelated to the large intestine. There is a complete disconnect between the mechanism claimed and the breadth of scope of the diseases allegedly treated by inducing proliferation or accumulation of Foxp3+ Tregs in the colon.

(326) In **AR6** the claims are limited to by reference to a formulation with a coating agent. There is no basis for adding yet another feature from the description to the claims creating yet further combinations of features. Furthermore, this amendment does nothing to address the issues of a lack of sufficiency or lack of inventive step as explained above in respect of the claims as granted.

(327) In **AR7** the claims are limited to the treatment of human subjects. There is no basis for adding yet another feature from the description to the claims. Furthermore, this amendment does nothing to address the issues of a lack of sufficiency, lack of novelty and lack of inventive step as explained above in respect of the claims as granted.

(328) In **AR8** the claims of AR7 have been further amended to specify the formulation of the composition as a capsule. Again, this adds a further feature to the claims that is not disclosed in

combination with the other features in the application as filed. Furthermore, the amendment does nothing to address the issues of lack of sufficiency or inventive step.

(329) **ARs 9-75** combine the amendments above from AR1-8. The same objections apply. The problems with added matter that arise from combining features are only made worse by combining further amendments taking features from disparate parts of the description.

(330) **ARs 76-79** were late filed and were not explicitly admitted into the proceedings by the OD.

(331) **AR76** includes the features of claim 2 in claim 1. For the reasons already explained above, the subject matter of claim 1 of AR76 adds matter, lacks novelty, lack inventive step and is not enabled.

(332) **ARs 77-79**: These ARs correspond to a combination of ARs 5 and 76 (AR 77); ARs 7 and 76 (AR 78), ARs 5 and 78 (AR 79). The objections raised above apply equally to these requests.

11. Conclusion

(333) The decision of the OD should be set aside and the patent should be revoked.

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