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Datasheet for the decision of 4 December 2023

Case Number: T 1076/20 - 3.3.07

Application Number: 11811267.1

Publication Number: 2658548

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Language of the proceedings: EN

Title of invention:
HUMAN MILK OLIGOSACCHARIDES FOR MODULATING INFLAMMATION

Patent Proprietor:
ABBOTT LABORATORIES

Opponents:
Société des Produits Nestlé S.A.
N.V. Nutricia

Headword:
Respiratory virus-induced inflammation/ABBOTT

Relevant legal provisions:
EPC Art. 83

Keyword:
Sufficiency of disclosure - (no)

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Case Number: T 1076/20 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 4 December 2023

Appellant: (Opponent 1)	Société des Produits Nestlé S.A. Entre-deux-Villes 1800 Vevey (CH)
Representative:	Plougmann Vingtoft a/s Strandvejen 70 2900 Hellerup (DK)
Appellant: (Opponent 2)	N.V. Nutricia Eerste Stationsstraat 186 2712 HM Zoetermeer (NL)
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Respondent: (Patent Proprietor)	ABBOTT LABORATORIES 100 Abbott Park Road Abbott Park, IL 60064-3500 (US)
Representative:	Boult Wade Tennant LLP Salisbury Square House 8 Salisbury Square London EC4Y 8AP (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 21 February 2020 rejecting the opposition filed against European patent No. 2658548 pursuant to Article 101(2) EPC**

Composition of the Board:

Chairman	M. Steendijk
Members:	J. Molina de Alba
	S. Ruhwinkel

Summary of Facts and Submissions

I. The decision under appeal is the opposition division's decision rejecting the two oppositions filed against European patent No. 2658548.

II. The patent was granted with seven claims. Claim 1 as granted read:

"*A synthetic pediatric formula for use in modulating respiratory virus-induced inflammation, the synthetic pediatric formula comprising a mixture of 3'-sialyllactose and 6'-sialyllactose in a concentration of 0.001 mg/mL to 20 mg/mL, wherein the 3'-sialyllactose is present in an amount of 0.001 mg/mL to less than 0.15 mg/mL*."

The compounds 3'-sialyllactose and 6'-sialyllactose will be abbreviated to 3'-SL and 6'-SL below.

III. The present decision makes reference to the following documents cited by the parties during the opposition and appeal proceedings:

D25 G. Duska-McEwen et al., Food and Nutrition Sciences, 5, 2014, 1383-95

D26 H.F. Rosenberg et al., Curr Med Chem, 19(10), 2012, 1424-31

IV. In the decision under appeal, the opposition division found, among other things, that the subject-matter of the claims as granted was sufficiently disclosed, novel and inventive.

V. Opponents 1 and 2 (appellants 1 and 2) each filed an appeal against the decision. With their statements of grounds of appeal, they filed new documents.

VI. With its reply to the statements of grounds of appeal, the patent proprietor (respondent) re-submitted the sets of claims filed as auxiliary requests 1 to 3 during the opposition proceedings.

Claim 1 of auxiliary request 1 was identical to claim 1 as granted.

Claim 1 of auxiliary request 2 differed from claim 1 as granted in that the concentration of the mixture of 3'-SL and 6'-SL was limited to **0.01** to 20 mg/ml.

Claim 1 of auxiliary request 3 differed from claim 1 of auxiliary request 2 in that the concentration of 3'-SL was limited to **0.01** to less than 0.15 mg/ml.

VII. With a letter dated 22 January 2022, appellant 1 filed an additional document.

VIII. The board scheduled oral proceedings, in line with the parties' requests, and gave its preliminary opinion on the case.

IX. Oral proceedings were held before the board on 4 December 2023. At the end of the oral proceedings, the board announced its decision.

X. The appellants' arguments relevant to the present decision can be summarised as follows.

The subject-matter of claim 1 as granted was not sufficiently disclosed. According to appellant 1, modulating inflammation encompassed both increasing and reducing inflammation. Therefore, claim 1 covered uses that did not provide any therapeutic benefit, namely those in which excessive inflammation was further increased.

Even if modulating inflammation was interpreted only as reducing inflammation, the invention would still be insufficiently disclosed. There were serious doubts as to whether a mixture of 3'-SL and 6'-SL according to claim 1 could reduce the inflammation induced by a respiratory virus in infants, toddlers and children. The only experimental evidence in the application as filed relating to the effect of the combination of 3'-SL and 6'-SL was in Example 40. Examples 39 and 40 also contained data concerning the effect of each of the individual compounds.

Example 40 was not suitable for proving the claimed effect. In fact, the effect derivable from Example 40 was the opposite of what the respondent sought to demonstrate. Figure 11 showed that virus infection did not give rise to an inflammatory response in the tested peripheral blood mononuclear cells (PBMCs). In contrast, 6'-SL and a mixture of 3'-SL and 6'-SL induced inflammation. Example 40 also demonstrated that the effect of a mixture was very different from the sum of the effects of the individual compounds. Therefore, the evidence related to each of the individual compounds was of no relevance when assessing the effect of the mixture.

Example 39 and Figures 3, 4, 7 and 8 illustrated that 3'-SL, at the concentrations defined in claim 1, had no anti-inflammatory effect in virus-infected PBMCs.

Post-published document D25 could not be used to demonstrate an effect that was not credible based on the application as filed. In any case, D25 did not demonstrate the claimed effect. Figure 6 of D25 showed that 3'-SL did not reduce the levels of inflammatory markers at concentrations higher than 0.05 mg/ml in virus-infected epithelial cells. As regards 6'-SL, Figure 7C of D25 showed that 6'-SL did not reduce the levels of IL-6 in virus-infected PBMCs and that it induced an inflammatory response in non-infected PBMCs. In addition, Figure 4 showed that 6'-SL did not reduce IL-6 levels in sub-bronchial gland cells at concentrations lower than 1 mg/ml. The first paragraph of page 1391 stated that 6'-SL reduced neither IP-10 nor TNFα levels in epithelial cells.

Therefore, there were serious doubts as to whether a mixture of 3'-SL and 6'-SL according to claim 1 could reduce the inflammation induced by a respiratory virus in infants, toddlers and children.

XI. The respondent's arguments relevant to the present decision can be summarised as follows.

Modulating inflammation within the meaning of the invention signified that inflammation was dampened, i.e. inflammation was reduced to levels that did not compromise control of an infection.

The subject-matter of claim 1 as granted was sufficiently disclosed. The appellants had not provided evidence raising serious doubts. It was necessary to

regard the data on file in its entirety rather than focusing on isolated examples. Examples 39 and 40 of the application as filed provided relevant evidence of the effect of 3'-SL, 6'-SL and mixtures thereof.

Example 39 and Figures 3, 4, 7 and 8 demonstrated that 6'-SL strongly reduced inflammation, even at very low doses. As regards 3'-SL, Figure 4 demonstrated that it suppressed IP-10 in a dose-dependent manner. This effect was confirmed by D25. Therefore, a product containing 3'-SL and 6'-SL could modulate inflammation.

Example 40 demonstrated the modulating effect of mixtures containing 3'-SL and 6'-SL. Figure 11 showed that the production of IL-8 was lower in infected cells treated with the mixture according to claim 1 (Combo 2) than in non-infected cells treated with the same mixture. This indicated that the mixture of claim 1 reduced inflammation in infected cells.

D25 confirmed the teaching of the application as filed. The results in D25, summarised in Table 2, demonstrated that 3'-SL and 6'-SL reduced several inflammatory markers in respiratory virus-infected epithelial cells and PBMCs.

In summary, the data on file proved that 3'-SL and 6'-SL generally reduced the production of pro-inflammatory cytokines and promoted anti-inflammatory cytokines in respiratory virus-infected cells. Therefore, it was credible that the synthetic formula of claim 1 could modulate the inflammation produced by a respiratory virus in infants, toddlers and children.

XII. The parties' final requests relevant to the present decision were as follows:

- The appellants requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

  Appellant 1 also requested that auxiliary requests 2 and 3, filed by the respondent during the opposition proceedings, not be admitted into the appeal proceedings.

- The respondent requested that the appeals be dismissed and that the opposition division's decision to maintain the patent as granted be upheld (main request).

  The respondent requested, in the alternative, that the patent be maintained in amended form on the basis of one of auxiliary requests 1 to 3 filed during the opposition proceedings.

Reasons for the Decision

1. Interpretation of the term "modulating"

1.1 Claim 1 of each of the requests on file refers to modulating the inflammation induced by a respiratory virus. The parties did not agree on the meaning of the term "modulating".

According to appellant 1, modulating generally encompassed both reducing and increasing. Therefore, the claims were not limited to reducing the inflammatory response induced by a respiratory virus. The claims also encompassed increasing inflammation, even if this led to a worsening a patient's condition instead of improving it.

The respondent considered that modulating the inflammation induced by a respiratory virus meant dampening it, i.e. reducing inflammation to an extent that does not compromise the ability to control the viral infection. This was particularly needed when treating respiratory-virus infections in infants, toddlers and children, since this patient population was prone to producing an excessively strong and persistent inflammatory response that could result in serious harm.

1.2 In the board's view, modulating generally means reducing or increasing according to needs, i.e. not arbitrarily.

Claim 1 as granted refers to a paediatric formula, i.e. a formula for administration to infants, toddlers and children. It was undisputed that the problem generally arising when infants, toddlers and children are infected with a respiratory virus is that they overreact, triggering an inflammatory response that can have profound negative consequences to the host (see, e.g., D26, abstract). Therefore, the main requirement in the context of claim 1 is to prevent the damage caused by excessive inflammation. Nevertheless, reducing the inflammatory response too much could compromise control of the infection. Consequently, the board agrees with the respondent that modulating

inflammation in claim 1 means dampening it, i.e. reducing inflammation to a level that prevents patient harm without compromising control of the infection. Achieving this balance between excessive and insufficient inflammation forms the basis for the therapeutic benefit on which the invention relies.

2. Sufficiency of disclosure (Article 100(b) EPC) - main request

2.1 Claim 1 as granted is drafted as a second medical use claim in accordance with Article 54(5) EPC. It is directed to a synthetic paediatric formula comprising a mixture of 3'-SL and 6'-SL at defined concentrations for use in modulating respiratory virus-induced inflammation.

It is established case law that the question to be answered when assessing sufficiency of disclosure of second medical use claims is whether or not the skilled person, having regard to the disclosure of a patent and common general knowledge at the relevant date of the application, would have considered that the active compound referred to in the claim was suitable to achieve the claimed therapeutic effect (Case Law of the Boards of Appeal, 10th edition, 2022, II.C.7.2.2; see also G 2/21, Reasons 74 and 77).

For the case in hand, this means that it is necessary to assess whether, in light of the application as filed and common general knowledge, the skilled person would have considered at the relevant date that the mixture of 3'-SL and 6'-SL at the concentrations defined in claim 1 was suitable for modulating respiratory virus-induced inflammation. Considering that the claim is directed to a paediatric formula, the effect should be

achievable in infants, toddlers and children, as taught in the application as filed (see, e.g., paragraphs [0002] and [0007]).

2.2 The only evidence on file relating to the effect of the mixture of 3'-SL and 6'-SL is in Example 40 of the application as filed. That example was intended to assess, *in vitro*, the ability of 3'-SL, 6'-SL and mixtures thereof to reduce the levels of pro-inflammatory cytokine IL-8 in PBMCs. 3'-SL and 6'-SL were tested as individual compounds at concentrations of 0.1, 0.2 and 0.5 mg/ml. They were also tested in combination at ratios of 1:1 (Combo1) and 1:2 (Combo2), with a total concentration of 0.2, 0.4 and 1.0 mg/ml. In the tests, PMBCs were infected with the respiratory syncytial virus (RSV). The results were presented in Figure 11.

2.2.1 The appellants correctly noted that Figure 11 (Lactose+RSV) shows that the infected control cells did not produce any substantial amounts of IL-8 when they were infected with RVS. For that reason alone, Example 40 is not a suitable model for assessing the ability of 3'-SL, 6'-SL and their mixtures to reduce inflammation. In fact, Figure 11 (Combo1, Combo1+RSV, Combo2, and Combo2+RSV) shows that the mixtures of 3'-SL and 6'-SL produce an inflammatory response rather than reducing such a response: their administration to infected or non-infected cells generated significant amounts of IL-8.

2.2.2 The respondent disagreed on this point for two reasons.

First, it noted that the levels of IL-8 produced by Combo2 decreased with increasing concentrations, and that the reduction in the IL-8 levels produced was more

pronounced in infected cells than in non-infected cells. Similarly, the levels of IL-8 produced by Combo1 when the concentration of 3'-SL was 0.1 mg/ml (i.e. as in claim 1) were also lower in infected cells than in non-infected cells. This supposedly demonstrated that a mixture of 3'-SL and 6'-SL was able to reduce inflammation in infected cells.

Second, Figure 11 demonstrated that the behaviour of a mixture of 3'-SL and 6'-SL with respect to IL-8 production was different from that of the individual compounds. Mixtures tended to produce less IL-8 with increasing concentrations, while the individual compounds had the opposite tendency. This also proved that a mixture of 3'-SL and 6'-SL could reduce inflammation.

2.2.3 The board disagrees.

With regard to the first reason, the fact that a mixture of 3'-SL and 6'-SL produces less inflammation in infected cells than in non-infected cells does not prove that it can reduce the inflammation caused by a viral infection. The fact that a substance causes less inflammation does not indicate that it can reduce the inflammation caused by another agent, such as a virus. The substance is still pro-inflammatory and there is no reason to assume that it could have anti-inflammatory properties.

With regard to the second reason, even if Figure 11 allowed the conclusion to be drawn that the levels of IL-8 produced by a mixture of 3'-SL and 6'-SL are lower than the levels produced by each of the compounds, added together, this would still give no indication as

to the ability of the mixtures to reduce the inflammation induced by a respiratory virus.

2.2.4 Therefore, Example 40 fails to prove that a mixture of 3'-SL and 6'-SL as defined in claim 1 can dampen the inflammation induced by a respiratory-virus infection.

2.3 The respondent also contended that the effect of the mixtures of 3'-SL and 6'-SL was not only demonstrated by Example 40. The evidence related to the anti-inflammatory effect of the individual compounds in Examples 39 and 40 of the application as filed and in post-published document D25 was also relevant and should be taken into account.

It is questionable whether the effect of the individual compounds can demonstrate the effect of their combination. Nevertheless, for the sake of completeness, the board has also analysed the evidence on the individual effects of 3'-SL and 6'-SL.

2.3.1 The effect of 3'-SL

Experimental evidence related to the effect of 3'-SL at the concentrations defined in claim 1, i.e. between 0.001 and 0.15 mg/ml, can be found in Example 39 (Figures 3, 4, 7 and 8) and Example 40 (Figure 11) of the application as filed as well as in Figure 6 of D25.

Example 39 set out the results of *in vitro* tests on PBMCs, in which two effects are assessed. Firstly, the ability of 3'-SL and 6'-SL to reduce the levels of pro-inflammatory cytokine IP-10 produced by RSV infection is assessed. Secondly, the ability of 3'-SL and 6'-SL to produce anti-inflammatory cytokine IL-10 in infected cells is assessed. Figures 3 and 4 (3SL+RSV vs

Lactose+RSV) show that the administration of 0.1 mg/ml 3'-SL produces IP-10 levels equivalent to those produced by the infected control. Similarly, Figures 7 and 8 (3SL+RSV vs Lactose+RSV) show that the administration of 3'-SL at 0.1 mg/ml does not result in IL-10 production. In other words, 3'-SL at the concentration required by claim 1 has no effect on IP-10 and IL-10.

Figure 11 (3SL+RSV and 3SL) of Example 40 shows that 3'-SL does not induce substantial amounts of IL-8 at 0.1 mg/ml.

D25 presents, in Figure 6, the results of *in vitro* tests in respiratory epithelial cells infected with RSV. The effect assessed was the ability of 3'-SL to reduce pro-inflammatory cytokines IL-6, IL-8 and MIP-1α, compared with the infected control (vehicle). According to Figure 6, there was a reduction in IL-6 and MIP-1α levels when 3'-SL was added at concentrations of between 0.005 and 0.050 mg/ml, and a reduction in IL-8 levels at concentrations of between 0.005 and 0.010 mg/ml. However, no effect was observed on any of the cytokines when 3'-SL was administered at concentrations of between 0.1 and 1.0 mg/ml, which overlaps with the concentration range defined in claim 1.

Therefore, the evidence on file demonstrates that 3'-SL has no effect on the assessed markers of inflammation across the concentration range defined in claim 1.

2.3.2 The effect of 6'-SL

Experimental evidence on the effect of 6'-SL when administered alone is also found in Example 39 (Figures

3, 4, 7 and 8) and Example 40 (Figure 11) of the application as filed. The relevant figures in D25 are Figures 4C and 7A to 7C. Claim 1 allows concentrations of 6'-SL from nearly zero to almost 20 mg/ml. As the 6'-SL concentration in the tests of Examples 39 and 40 and in D25 is never higher than 1 mg/ml, all the results presented for 6'-SL are relevant.

Example 39 shows, in Figures 3 and 4 (6SL+RSV vs Lactose+RSV), that 6'-SL reduces the levels of pro-inflammatory cytokine IP-10 in RSV-infected PBMCs. Similarly, Figures 7 and 8 show that 6'-SL induces the production of anti-inflammatory cytokine IL-10 (6SL+RSV vs Lactose+RSV).

Figure 11 (6SL+RSV vs Lactose+RSV) of Example 40 shows that 6'-SL induces the production of pro-inflammatory cytokine IL-8 in RSV-infected PMBCs. The effect grows with increasing 6'-SL concentrations.

D25 shows in Figure 4C that 6'-SL, administered at doses of 0.01 or 0.10 mg/ml, does not reduce the levels of pro-inflammatory cytokine IL-6 induced by RSV-infection in respiratory epithelial cells. An effect is observed at 1 mg/ml. Figures 7A to 7C relate to the effect of 6'-SL on pro-inflammatory cytokines IP-10, TNFα and IL-6 in RSV-infected PBMCs. Figures 7A and 7B show that 6'-SL reduces IP-10 and TNFα levels in a dose-dependent manner, compared to the control. Figure 7C, however, shows that 6'-SL has no effect on IL-6 at the tested concentrations (0.01 to 1.0 mg/ml).

In conclusion, the effect of 6'-SL on pro-inflammatory cytokines in RSV-infected PMBCs is as follows: it increases IL-8, has no effect on IL-6, and reduces IP-10 and TNFα. The compound 6'-SL also induces

production of anti-inflammatory cytokine IL-10. As regards respiratory epithelial cells, no effect was observed on IL-6 at concentrations of 0.1 mg/ml or below.

2.4 It has been explained in the context of claim interpretation that modulating inflammation in claim 1 means reducing the inflammation caused by the virus infection to a level that prevents harm to the patient but does not compromise infection control. The evidence on file does not allow the conclusion to be drawn that the mixtures of 3'-SL and 6'-SL according to claim 1 are suitable for allowing this balance to be achieved between reducing excessive inflammation and maintaining functional levels of the immune response. The balance is certainly not achieved across the concentration ranges defined in claim 1. Firstly, no anti-inflammatory effect has been demonstrated for the mixtures of 3'-SL and 6'-SL. On the contrary, the mixtures appear to produce a pro-inflammatory cytokine. Secondly, 3'-SL has no effect on cytokine production, at least not in part of the concentration range defined in claim 1. Thirdly, 6'-SL has been shown to influence cytokine levels in a way that produces opposing effects. It can both promote and reduce inflammation, but the balance of these opposing effects is unknown. That uncertainty is confirmed by the teaching in D26 (page 4, second paragraph, last few lines) - referred to by the respondent in the oral proceedings before the board - that there is no consensus on which cytokine is the critical mediator of the immune response to a respiratory-virus infection.

Therefore, the board has serious doubts as to the ability of the mixtures of 3'-SL and 6'-SL according to claim 1 to modulate the inflammation caused by a

respiratory-virus infection in infants, toddlers and children. The skilled person would not be able to ascertain, without undue burden, which mixtures according to claim 1, if any, produce the claimed therapeutic effect.

Consequently, the subject-matter of claim 1 is not sufficiently disclosed and the ground for opposition of Article 100(b) EPC precludes the maintenance of the patent as granted.

3. *Sufficiency of disclosure (Article 83 EPC) - auxiliary requests 1 to 3*

Claim 1 of auxiliary request 1 is identical to claim 1 of the main request. Therefore, its subject-matter is not sufficiently disclosed, for the same reasons as those indicated for the patent as granted.

In auxiliary requests 2 and 3, claim 1 has been further limited by raising the lower limit of the corresponding concentration ranges from 0.001 to 0.01 mg/ml. Irrespective of the issue of admittance, the reasons provided to explain why the subject-matter of claim 1 as granted is insufficiently disclosed apply equally to the subject-matter of claim 1 of auxiliary requests 2 and 3.

Therefore, none of the auxiliary requests on file meets the requirements of Article 83 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos M. Steendijk

Decision electronically authenticated