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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte STEVEN CHARLES HODGKINSON,
CHRISTOPHER PAUL MCJARROW,
MURRAY D. MITCHELL, ANGELA MARIE ROWAN,
JOANNE MARGARET TODD, and
MARK HEDLEY VICKERS[1]

Appeal 2019-004320
Application 12/682,582
Technology Center 1600

Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and JOHN G. NEW, *Administrative Patent Judges.*

NEW, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1]We use the word "Appellant" herein to refer to the "applicant" as defined in 37 C.F.R. § 1.142. Appellant identifies Fonterra Co-Operative Group Limited as the real party-in-interest. App. Br. 3.

SUMMARY

Appellant files this appeal under 35 U.S.C. § 134(a) from the Examiner's Final Rejection of claims 32–34, 45, 47–51, 53, 54, and 56–65 as unpatentable under 35 U.S.C. § 103 as being obvious over the combination of Shulman et al. (WO 2006/114790 A2, November 2, 2006) ("Shulman '790"), Shulman et al. (WO 2005/051091 A1, June 9, 2005) ("Shulman '091"), Fletcher et al. (WO 2006/041316 A1, April 20, 2006) ("Fletcher"), and Beermann et al. (WO 2006/019300 A2, February 23, 2006) ("Beermann").

We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

NATURE OF THE CLAIMED INVENTION

Appellant's invention is directed one or more complex lipids, including gangliosides, to achieve particular health benefits including maintaining or increasing cognitive development or maintaining or increasing growth in a fetal, infant, or child subject. Abstr.

REPRESENTATIVE CLAIM

Claim 32 is representative of the claims on appeal and recites:

> 32. A method for maintaining or increasing cognitive development of a foetal, infant, or child subject by orally administering a composition formulated to comprise comprising one or more complex lipids to a mother during gestation or an infant or child subject in need thereof, wherein the one or more complex lipids comprises one or more gangliosides, and wherein the composition comprises up to 19 grams of the one or more complex lipids per 100g on a dry basis and at least 8 mg gangliosides per 100g on a dry basis, and wherein the one or

> more gangliosides comprises GM3, GD3, or a mixture of at least GM3 and GD3.

App. Br. 21.

ISSUES AND ANALYSES

We adopt the Examiner's findings, reasoning, and conclusion that the claims on appeal are obvious over the prior art cited by the Examiner. We address the arguments raised by Appellant below.

Issue 1

Appellant argues that the Examiner erred in finding that the combined cited prior art teaches or suggests the use of gangliosides as constituents of the claimed composition or as improving or maintaining cognitive development. App. Br. 10.

Analysis

The Examiner finds that Shulman '790 teaches compositions comprising phospholipids, including sphingomyelin, from milk for infants and young children and pregnant women. Final Act. 3 (citing Shulman '790 10). The Examiner finds that the compositions of Shulman '790 can contain a wide percentage range of polar lipids, including phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, and sphingomyelins. *Id.* (citing Shulman '790 13, 24–27). The Examiner finds that Shulman '790 teaches that these constituents are known to play a very important role in the nutrition of developing infants and are useful for

enhancement of infants' and/or childrens' development, particularly cognitive development. *Id.* at 4 (citing Shulman '790 1, 16, 17, 28, 30, 31).

The Examiner finds that Shulman '790 does not expressly teach gangliosides as components as constituents of its compositions. Final Act. 4. However, the Examiner finds that Shulman '091 teaches that human milk fat has all of the ingredients claimed in Appellant's composition and that phospholipids show a variety of health benefits which include improvement of cognitive functions, and contribution to general well-being of infants, young children, and pregnant women, and enhancement of fetal development. *Id.* (citing Shulman '091 1–5, 11, 16, 42).

The Examiner finds that Fletcher teaches compositions comprising complex lipids including at least 0.1 % w/w ganglioside GD3, sphingomyelin, and phospholipids. Final Act. 4 (citing Fletcher 24, Table 6). The Examiner finds that Fletcher further teaches that the composition can also contain sphingolipids. *Id.* (citing Fletcher 5). The Examiner finds that the ingredients are obtained from milk fat globules via extraction. *Id.* (citing Fletcher 9, 13, 14). The Examiner finds that compositions A–D of Fletcher, as disclosed in Table 6, consist of about 52% lipids, about 23–31% phospholipids, about 5–8% phosphatidylcholine, about 6–9% phosphatidylethanolamine, about 2–3% of phosphatidylserine, about 1–2% phosphatidylinositol, about 6–7% sphingomyelin and 1% gangliosides. *Id.* at 4–5 (*see also* Fletcher 1). The Examiner finds that the compositions of Fletcher produces health benefits for infants and children. *Id.* at 5 (citing Fletcher 9, 13). The Examiner also finds that Fletcher teaches that increasing the levels of phospholipids and glycosphingolipid in infant formulations to the levels found in human milk (particularly gangliosides

GM3, GD3, ceramides and sphingomyelin) lead to optimal neural development, and that it is therefore desirable to produce infant formula containing sufficient amounts of these desirable lipids. *Id.* (citing Fletcher 1–2). The Examiner therefore reasons that Fletcher suggests to the skilled artisan the inclusion of gangliosides GM3 and GD3 in the composition of Shulman '091, because Shulman '091 teaches the same constituents as Fletcher and the same purpose in providing health benefits, and also teaches adjusting the amounts of the complex lipids, including gangliosides. *Id.*

The Examiner finds that Beermann is directed to infant formulae, and teaches that gangliosides are a preferable component in its formulae. Final Act. 5 (citing Beermann 4). The Examiner finds that Beermann teaches gangliosides preferably present at between 0.1 and 10 grams per 100g dry weight in the composition. *Id.* (citing Beermann 5).

The Examiner concludes that it would have been obvious to a person of ordinary skill in the art to make the claimed compositions and use them in the claimed methods, because the ingredients recited in the instant claims are taught in the prior art to be individually useful for increasing and/or maintaining the cognitive development and growth of fetal, infants and children. Final Act. 6. The Examiner reasons that a skilled artisan would have been motivated to make and use the compositions in the claimed methods since they are obtained from easily available sources, such as milk dairy products, and because increasing the level of phospholipid and ganglioside levels in infant formulations have beneficial effects in addition to enhancing/improving cognitive effects and growth in fetuses, infants and young children, as taught by Shulman '091 and Fletcher, and because

compositions comprising gangliosides also offer protection against allergies and infection. *Id.* (citing Beermann Abstr.).

Finally, the Examiner concludes that it would have been well within the level of skill of one skilled in the art to adjust the amounts of the components in the compositions taught by the references, so as to optimize the beneficial effects based on the teachings of the prior art. Final Act. 7.

Appellant first notes that, on July 13, 2015, the Examiner issued a Notice of Allowability (the "Notice") in view of Appellant's prior submissions, acknowledging that the method claims were not obvious over Fletcher, Shulman '790, and Shulman '091. App. Br. 9. According to Appellant, the Examiner acknowledged that Fletcher does not teach or suggest using its composition in a method for maintaining or increasing cognitive development. *Id.* at 9–10 (citing Notice 6–7). Appellant asserts that the Examiner also acknowledged that neither Shulman '790 nor Shulman '091 teach the use of gangliosides as components in their compositions, and that these references do not teach that gangliosides improve or maintain cognitive development. *Id.* at 10. Specifically, Appellant notes that the Examiner stated:

> There is no teaching, suggestion or motivation in the combined teachings of the cited prior art to administer orally a composition comprising at least 8mg gangliosides per 100g on a dry basis in the claimed methods of improvement or maintenance of cognitive development in a foetal, infant, or child subject as instantly claimed.

Id. at 10 (quoting Notice 7). Appellant contends that there is no new evidence that the references teach or suggest the claimed methods, or that the cited references discloses a composition comprising at least

8mg gangliosides per 100 g on a dry basis for use in a method for improvement or maintenance of cognitive development in a foetal, infant, or child subject, as recited by independent claims 32 and 34. *Id.*

Specifically, Appellant argues that Shulman '790 does not teach the inclusion of gangliosides in a composition or suggest that gangliosides have any role in cognitive development of a fetal, infant, or child subject. App. Br. 10. Rather, argues Appellant, Shulman '790 teaches "polar lipid preparations, in particular mixtures comprising glycerophospholipids, optionally with sphingomyelin." *Id.* (citing Shulman '790 1). Appellant asserts that gangliosides are neither glycerophospholipids nor sphingomyelin, and the effect of these components on cognitive development is irrelevant to Appellant's independent claims 32 or 34, which relate to complex lipids comprising one or more gangliosides. *Id.*

Appellant contends that, similarly, Shulman '091 does not teach compositions including gangliosides, or any discussion of the role gangliosides perform in cognitive development. App. Br. 10. Appellant points to the Examiner's finding that Shulman '091 teaches that "phospholipids show a variety of health benefits which include improvement of cognitive functions and contribution to general well-being." *Id.* at 10–11 (quoting Final Act. 4). Appellant contends that, whether phospholipids have any effect on cognitive development of infants or children is irrelevant to the pending claims, as gangliosides are not phospholipids. *Id.* at 11.

Appellant argues that, although Fletcher teaches the inclusion of gangliosides in infant formulas, it fails to link a composition including gangliosides to a method for improving or maintaining cognitive development of a fetal, infant, or child subject. App. Br. 11. Appellant

points to the Examiner's finding that Fletcher teaches that: "Research over the last 5–10 years has shown that increasing phospholipid and (glyco)sphingolipid levels in infant formulations to levels found in human milk (particularly ganglioside GM3, ganglioside GD3, ceramides and sphingomyelin) may lead to: … optimal neural development." *Id.* at 11 (quoting Fletcher 1–2).

Appellant contends that this teaching of Fletcher is deficient for three reasons. App. Br. 11. First, Appellant argues, Fletcher fails to link any specific components of the formulations to any specific benefit. App. Br. 11. Appellant asserts that there is no specific linking of gangliosides to any benefit but, rather, only a linking of the entire formulation, including sphingomyelin and ceramides, to neural development. *Id.* According to Appellant, any of the various components could be alleged to be responsible for optimal neural development. *Id.* As such, argues Appellant, Fletcher fails to provide a reason to select not only the specific combination but also the amounts of gangliosides recited in claims 32 and 34. *Id.*

Second, Appellant argues that, even if gangliosides had been linked directly to neural development by Fletcher, the specific amount claimed in the present application is not. Final Act. 11. Third, Appellant contends, neural development is an extremely vague term that is undefined in Fletcher and is not synonymous with cognitive development, as recited in the claims on appeal. *Id.* Appellant asserts that: "Neural development could refer to a dissimilar array of aspects of neural structures and functions, including birth of neurons, migration of neurons, neuron connection, neuron receptors, synaptic formation and plasticity, birth of glia, myelination, muscle control, sensation, or autonomic function, or others." *Id.* at 12. In contrast,

Appellant points to the Specification's disclosure that: "The terms 'increasing cognitive development' or 'to increase cognitive development' are used interchangeably herein and refer to increasing the rate, ability, interest, willingness, or openness to learn, remember or apply knowledge. In some embodiments, 'cognitive development' refers to brain weight and brain ganglioside content." *Id.* (quoting Spec. ¶ 59).

Appellant argues further that the Examiner acknowledges that "Fletcher does not teach … enhancement/maintenance of cognitive development." App. Br. 12 (quoting Final Act. 10). Appellant therefore contends that, because Fletcher fails to explicitly link gangliosides with cognitive development, as that term is defined in Appellant's Specification, the teaching of Fletcher do not cure the alleged deficiencies of Shulman '790 and Shulman '091. *Id.* Rather, Appellant argues, the Examiner is impermissibly relying on hindsight analysis by using the disclosures of Appellant's Specification as a roadmap to arrive at the claimed methods. *Id.*

With respect to Beermann, Appellant argues that the reference is merely cumulative to the other art of record, at least with respect to Fletcher, and fails to cure the alleged deficiencies in the other references. App. Br. 12. According to Appellant, Beermann's teaching that its composition preferably comprises between 0.1 and 10 grams acidic oligosaccharides per 100 gram dry weight of the composition is not an indication that gangliosides may be included in this amount. *Id.* Appellant contends that the acidic oligosaccharide comprises at least one acidic group selected from a specific list, and although N-acetylneuraminic acid (which is a component of gangliosides) is listed as one of the acidic groups, Appellant asserts that there is no mention of gangliosides in the discussion of acidic

oligosaccharides. *Id.* at 12–13. Appellant also contends that Beermann fails to teach that the formula therein can be used to improve or maintain cognitive development, as recited by the claims. *Id.* at 13.

Finally, Appellant argues, the Examiner did not properly assert that the amount of gangliosides is a result-effective variable, because the cited art does not recognize any specific relationship between gangliosides and cognitive development. App. Br. 13. Appellant contends that a result-effective variable is not simply a variable that can be optimized, but must rather be shown to achieve a recognized result. *Id.* (citing, e.g., MPEP § 2144.05(II)(B); *In re Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977). Appellant argues that, other than asserting that the amount of ganglioside "can be optimized," the Examiner did not establish that the amount of ganglioside is, in fact, a result-effective variable. *Id.*

We are not persuaded by Appellant's arguments. As an initial matter, the fact that the Examiner issued, on July 13, 2015, a Notice of Allowability for the claims on appeal is of no moment in our analysis. If the Examiner makes a determination different from a determination previously made during prosecution, that is permissible so long as it is properly grounded, as here, in the evidence of record. *See In re Ruschig*, 379 F.2d 990, 992–993 (C.C.P.A. 1967) ("There is nothing unusual, certainly, about an examiner changing his viewpoint as to the patentability of claims as the prosecution of a case progresses, and, so long as the rules of Patent Office practice are duly complied with, an applicant has no legal ground for complaint because of such change in view").

We acknowledge that neither Shulman '790 nor Shulman '091 expressly teach gangliosides, including those specifically recited in the

independent claims. However, Shulman '091 is directed to: "[A] substantially homogenous lipid preparation comprising a combination of glycerophospholipids being phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS) and phosphatidylinositol (Pl), wherein the quantitative ratio between said glycerophospholipids essentially mimics their corresponding ratio in naturally occurring human milk fat (HMF)." Shulman '091 p. 11. Shulman '091 also teaches that: "In a preferred embodiment, the lipid combination of the invention optionally further comprising sphingomyelin (SM) and/or cholesterol, wherein the quantitative ratio between the glycerophospholipids in said combination and the sphingomyelin and/or cholesterol essentially mimics their corresponding ratio in said naturally occurring HMF." *Id.* Shulman '091 further teaches that "[t]he amount of phospholipids (sphingomyelin and glycerophospholipids) in human milk fat is about 15-20 mg/dL" and that "[s]ome phospholipids, and especially those extracted from soybean, are used as dietary supplements and a variety of health benefits are associated with their intake. These benefits include the improvement of cognitive functions, improvement of memory and concentration, maintenance of cellular membrane composition, and contribution to general well-being." *Id.* at 4.

> Similarly, Shulman '790 teaches:
>
> In [Shulman '091], the inventors used pure bovine milk sphingomyelin, obtainable as an analytical standard or research chemical, which is not particularly suitable for use in infant nutrition or dietary supplements due to its high cost and extremely low availability, as mentioned previously.
>
> Thus, it is a purpose of the current invention to provide polar lipid preparations mimicking the polar lipids of HMF, optionally comprising [sphingomyelin], wherein the source of said polar lipids is a natural non-brain lipid source.
>
> It is another object of the present invention to provide a dietary supplement which guarantees the sufficient and recommended intake of phospholipids, especially of PS and sphingomyelin, in the form of a mimetic substitute of the phospholipids from human breast milk lipid, aimed especially for infants and young children consumption, as well as pregnant women.

Shulman '790 p. 10. Shulman '790 also teaches that: "Still further, the lipid mixtures and preparations of the invention and the dietary supplements, nutrients or food articles comprising them may be used in the enhancement of infants and/or children development, particularly cognitive development and/or in the enhancement of vision development." *Id.* at 16.

> Fletcher teaches that:
>
> [S]tandard infant formulas are typically produced using low-fat dairy products such as skim milk. Using a reduced-fat dairy product means undesirable components in milk fat are not included in the infant formula, but it also means that phospholipid and (glyco)sphingolipid levels are significantly lower than those in human milk.
>
> Research over the last 5-10 years has shown that increasing phospholipid and (glyco)sphingolipid levels in infant formulations to levels found in human milk (particularly

> ganglioside GM_3, ganglioside GD_3, ceramides and sphingomyelin) may lead to:
>
> - enhanced gut maturation, thereby reducing the risk of infection;
> - prevention of infections by modifying gut intestinal flora and competitively binding antigens;
> - prevention of the development of allergies; and
> - optimal neural development.
>
> It is therefore desirable to produce an infant formula containing sufficient levels of desirable lipids while minimising or eliminating undesirable ingredients.

Fletcher 1–2.[2]

Table 6 of Fletcher shows the lipid composition of its exemplary products A-E:

[2] It is useful to point out at this juncture that the gangliosides present in human milk fat recited in Appellant's claims on appeal are (glyco)sphingolipids closely related to the sphingomyelin recited in Shulman '790 and Shulman '091, sharing the same N-acetylneuraminic acid – saturated lipid chain, but with a phosphate group in sphingomyelin and multiple cyclic carbohydrates in gangliosides. *See Sphingolipids - Chemistry and Biochemistry: An Introduction*, *available at*: https://www.lipidhome.co.uk/lipids/sphingo/introsph/index.htm (last visited May 29, 2020).

Table 6 - Polar lipid compositions of products A-E

Component (% w/w)	A	B	C	D	E
Total lipid	20.6	33.9	20.9	86.1	6.3
Total phospholipid	9.7	15.1	17.5	66.6	5.2
Phosphatidylcholine	2.6[1]	4.1	4.9	13.3	1.7
Phosphatidylethanolamine	2.7[1]	4.2	4.8	22.0	1.0
Phosphatidylserine	0.8[1]	1.3	1.7	8.2	0.36
Phosphatidylinositol	0.6[1]	1.0	1.2	6.1	0.35
Sphingomyelin	2.7[1]	4.2	4.4	15.1	1.8
Ganglioside GD3	0.36	0.58[2]	0.66[3]	2.09	0.28
Ganglioside GM3	0.04	0.06[2]	0.05[3]	0.34	0.0

Table 6 of Fletcher shows the lipid compositions of its exemplary products A-E

We note here that Table 6 of Fletcher lists, as constituents of its "Total Lipids" those phospholipids taught by Shulman '790 and '091, *viz.*, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol (*see, e.g.*, Shulman '091 4), and sphingomyelin, as well as gangliosides GD3 and GM3.

We agree with the Examiner that a person of ordinary skill in the art would have recognized, from the combined teachings of Shulman '790, Shulman '091, and Fletcher that gangliosides, together with phospholipids and sphingomyelin, are constituents of human milk fat. A skilled artisan would also understand that whereas Shulman '790 and Shulman '091 teach that its compositions, which approximate the lipid content of human milk fat maintain and increase cognitive development in fetuses, infants, and children, Fletcher teaches that its compositions promote at least "optimal neural development" which would include within its scope "maintain[ing] and increase[ing] cognitive development" that is also promoted by the

phospholipids and sphingomyelin that are taught by both Fletcher and the Shulman references.

Beermann is also directed to "a nutritional composition … particularly suited for feeding infants as it mimics the protective effects of human milk." Beermann, Abstr. In relevant part, Beermann teaches:

> Preferably the NCC [negatively charged non-proteineous glycan and glycoconjugate component] is selected from the group consisting of glycosphingolipids, *acid oligosaccharides*, and sialysated oligosaccharides. Preferably the sialysated oligosaccharides is sialyllactose and/or disialo-lactoneotertaose (DS-LNT). Glycosphingolipids are typically compounds with a monosaccharide attached directly to a ceramide.
>
> Preferably the NCC contains a ganglioside (a glycosphingolipid). Gangliosides are typically highly complex oligoglycosylceramides, which contain one or more sialic acid groups (*N*-acyl, especially acetyl, derivatives of neuraminic acid, abbreviated to "NANA") in addition to glucose, galactose and galactosamine. For this application, especially buttermilk, egg yolk lecithin are suitable raw material sources of gangliosides. Hence the present composition preferably contains egg yolk lecithin and/or buttermilk.
>
> In a particularly preferred embodiment the present composition contains a ganglioside selected from the group consisting GM3, GM1 and GD1.

Beermann 4 (emphasis added, external reference omitted). Beermann further teaches that, with respect to the acid oligosaccharides mentioned in the passage quoted *supra*: "The present composition preferably contains between 0.1 and 10 grams acid oligosaccharides per 100 gram dry weight of the present composition, more preferably between 1 and 6 grams per 100

gram dry weight." *Id.* at 5.[3] As disclosed by the Specification, therefore, the acid oligosaccharides of the gangliosides (i.e., sialic acid groups (N-acyl, especially acetyl, derivatives of neuraminic acid, abbreviated to "NANA" in addition to glucose, galactose and galactosamine) constitutes between 0.1 and 10 grams per 100 grams dry weight of the composition.

Because the oligosaccharides constitute a substantial portion of the mass of the ganglioside, we agree with the Examiner that the range taught by Beermann encompasses Appellant's claimed range of gangliosides. *See In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) (holding that "[i]n cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness"). We consequently agree with the Examiner that the

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[3] For the sake of clarity, gangliosides are defined thus:

> Glycolipids are biomolecules containing one or more carbohydrate residues linked to a hydrophobic lipid moiety through a glycosidic linkage. Glycolipids containing either a sphingoid or a ceramide as the hydrophobic lipid moiety are referred to as glycosphingolipids.… Acidic glycosphingolipids containing one or more sialic acid (N-acetylneuraminic acid or N-glycolylneuraminic acid) residue(s) in their carbohydrate moiety are especially referred to as gangliosides. Figure 1 depicts a common brain ganglioside, GM1.

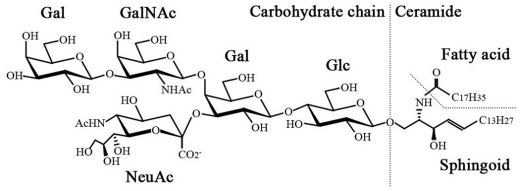

Figure 1 of Yu depicts the structure of ganglioside GM1

R.K. Yu et al., *Structures, biosynthesis, and functions of gangliosides—An overview*, 60(10) J. OLEO. SCI. 537–44 (2011).

combined cited prior art references teach or suggest the limitations of the claims on appeal.

Finally, with respect to Appellant's argument that the Examiner did not properly assert that the amount of gangliosides is a result-effective variable, because the cited art does not recognize any specific relationship between gangliosides and cognitive development (see App. Br. 13), Fletcher teaches that "Research over the last 5–10 years has shown that increasing phospholipid and (glyco)sphingolipid levels in infant formulations to levels found in human milk (particularly ganglioside GM3, ganglioside GD3, ceramides and sphingomyelin) may lead to: … optimal neural development." Fletcher 1–2. We agree with the Examiner that a person of ordinary skill in the art could reasonably infer from this teaching that the levels of gangliosides, including gangliosides GM3 and GD3 are related to the level of cognitive development in infants and is consequently a result-effective variable, and that increasing the levels of ganglioside present in formulae to levels approaching that found in normal human breast milk would yield improved cognitive function compared to formulae that were comparable deficient in these ganglosides.

Issue 2

Appellant argues the Examiner erred because there would have been no reason to combine the references to arrive at Appellant's claimed invention. App. Br. 14.

Analysis

Appellant argues that, not only is there no specific reason to modify the references cited by the Examiner to arrive at Appellant's claimed invention, the references explicitly teach away from modification in the manner asserted by the Examiner. App. Br. 14.

In support of these contentions, Appellant points to the Declarations of Alastair MacGibbon, filed September 12, 2014 (the "MacGibbon Declaration") and of Ronald Schnaar, filed September 12th, 2014 (the "Schnaar Declaration"). App. Br. 14. According to Appellant, the MacGibbon and Schnaar Declarations set out reasons why a person of skill in the art would not have combined Shulman '790, Shulman '091 and Fletcher, identifying teachings away from the asserted combination. *Id.* According to Appellant, the MacGibbon and Schnaar Declarations establish that the various lipid concentrations and processes by which lipids are obtained is relevant to whether a person of skill in the art would have read Shulman '790, Shulman '091 and Fletcher together. *Id.*

> Appellant points to the Schaar Declaration as opining that:
>
> The procedures used by Fletcher to generate their products involved treating beta-serum with near critical CO_2. These conditions are clearly not the same as those used to obtain the lipid extracts of [Shulman] '790 or '091. So it is not evident that products obtained by these different processes would have the same specific components or provide the same benefits. For at least this reason, I would not have combined Fletcher with '790 or '091.

App. Br. 14 (quoting Schaar Decl. ¶ 57).

Appellant similarly cites the MacGibbon Declaration as explaining the various reasons why a person skilled in the art would not have combined either Shulman '790 or Shulman '091 with Fletcher. App.Br. 14. Appellant notes that MacGibbon opines that: "At page 8, second paragraph, [Shulman] '790 criticizes certain preparations such as those of Fletcher, as containing phospholipid concentrations that are too low and containing undesirable proteins and carbohydrates." App. Br. 14 (quoting MacGibbon Decl. ¶ 10). Similarly, argues Appellant, the MacGibbon Declaration opines that: At page 8, third paragraph, [Shulman] '790 states that the ratio of phospholipids in certain products such as those of Fletcher is undesirable, being too low in sphingomyelin relative to other phospholipids, and containing too much non-phospholipid material." *Id.*

Appellant contends that the Schnaar and MacGibbon Declarations provide evidence that the formulations of Shulman '790 and Fletcher are incompatible and that Shulman '790 teaches away from utilizing phospholipid concentrations at the levels found in Fletcher. App. Br. 14–15. Furthermore, Appellant argues, the ratio of the various phospholipids in Fletcher are irreconcilable with the teachings of Shulman '790. *Id.* (citing

MacGibbon ¶ 11). Appellant asserts that the MacGibbon Declaration attests that preparations, such as those in Fletcher, would be incompatible with Shulman '790 because they contain phospholipid concentrations that are too low, contain undesirable proteins and carbohydrates, contain an undesirable ratio of phospholipids, particularly sphingomyelin relative to other phospholipids, and contain too much nonphospholipid material. *Id.* (citing MacGibbon Decl. ¶¶ 10–17).

Turning to Beermann, Appellant argues that Beermann teaches that its compositions provide protective effects against allergies and infection and stimulates the development of the nervous system of neonates, but Appellant contends that there is no indication that it increases cognitive development. App. Br. 15 (citing Beermann Abstr.). Furthermore, contends Appellant, Beermann provides no evidence to substantiate any utility of its described compositions. *Id.* As a result, Appellant asserts, there would have been no reason to combine Beermann with the other references and to modify its teachings as asserted by the Examiner. *Id.*

We are not persuaded by Appellant's arguments. The Schnaar Declaration opines that:

> The procedures used by Fletcher to generate their products involved treating beta-serum with near critical CO_2. These conditions are clearly not the same as those used to obtain the lipid extracts of [Shulman] '790 or '091. So it is not evident that products obtained by these different processes would have the same specific components or provide the same benefits. For at least this reason, I would not have combined Fletcher with [Shulman] '790 or '091.

Schnaar Decl. ¶ 57. We do not find this persuasive. Shulman '091 teaches compositions comprising a combination of phospholipids (*viz.*,

phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol) and sphingomyelin. *See* Shulman '091 13. Fletcher teaches compositions comprising the elements listed in Shulman '091 together with gangliosides GD3 and GM3. *See* Fletcher Table 6. Even acknowledging Dr. Schnaar point that the compositions of Shulman '091 and '790 were synthesized by a different method from that of Fletcher, the Schnaar Declaration provides no evidence of record to show that identical constituents of a nutritional composition (the phospholipids and sphingomyelin), although synthesized by different means, would not have the same beneficial nutritional effects.

The MacGibbon Declaration states that:

> [Shulman] '790 clearly indicates that certain known compositions comprising polar lipids are undesirable to use. At page 8, second paragraph, [Shulman] '790 criticises certain preparations such as those of Fletcher, as containing phospholipid concentrations that are too low and containing undesirable proteins and carbohydrates. At page 8, third paragraph, [Shulman] '790 states that the ratio of phospholipids in certain products such as those of Fletcher is undesirable, being too low in sphingomyelin relative to the other phospholipids, and containing too much non-phospholipid material.

MacGibbon Decl. ¶ 10. Shulman '790 teaches that:

> [T]he dairy industry has started to utilize dairy waste to produce nutritional preparations which contain milk proteins, carbohydrates and small amounts of lipids. The latter include neutral lipids as well as polar lipids, including glycerophospholipids as well as sphingolipids, among them sphingomyelin. These preparations contain extremely low levels of sphingomyelin and phosphatidylserine, making them incompatible as an industrial source for these nutrients.

Shulman '790 8. It is by no means evident that the nutritional preparations produced by "the dairy industry" includes the preparations of Fletcher, but it is immaterial of they do. In an obviousness analysis:

> The test … is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.

In re Keller, 642 F.2d 413, 425 (C.C.P.A. 1981). The issue, then is not whether the compositions of Fletcher could be physically combined with those of Shulman '790 and/or '091, but is rather what the combined teachings of the references would have suggested to a person of ordinary skill. We conclude that a person of ordinary skill in the art, upon comprehending the teachings of Shulman '790 that extremely low levels of sphingomyelin and phospholipids are "incompatible as an industrial source for these nutrients" would have been motivated to combine the teachings of Shulman '790 and '091 with Fletcher to achieve higher concentrations of phospholipids and sphingomyelin, along with the ganglioside concentrations taught by Fletcher.

The MacGibbon Declaration further states that "[i]n view of these passages, I would not have considered the extracts of Fletcher to be polar lipid preparations within the scope of '790." MacGibbon Decl. ¶ 13. But whether the teachings of Fletcher are "within the scope of" the teachings of Shulman '790 (or '091) is irrelevant to our obviousness analysis. What is relevant, again, is what the *combined* teachings of the references would suggest to a person of ordinary skill in the art. *Keller*, 642 F.2d at 425. One

cannot show non-obviousness by attacking references individually where … the rejections are based on combinations of references." *Id.* at 426.

We are therefore not persuaded that a person of ordinary skill in the art would have had no reason to combine the teachings of Shulman '790 and '091 and Fletcher. Nor are we persuade that there is a teaching away from Appellant's claimed invention in the cited prior art. A reference teaches away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Appellant points to no evidence of record teaching or suggesting that the compositions taught by Shulman '790, Shulman '091, Fletcher, and Beermann could not be combined, specifically, that the high concentrations of phospholipids and sphingomyelin taught by Shulman '790 could not be combined with the gangliosides taught by Fletcher. Appellant points to, with no evidence of record that would discourage or divert a skilled artisan from combining the references.

Finally with respect to Fletcher and Beermann, Fletcher teaches that: "Research over the last 5-10 years has shown that increasing phospholipid and (glyco)sphingolipid levels in infant formulations to levels found in human milk (particularly ganglioside GM3, ganglioside GD3, ceramides and sphingomyelin) may lead to…optimal neural development." Fletcher 1–2. Beermann teaches "The present nutritional composition is particularly effective in … [s]timulating the development of the nerve system of neonates. Beermann 1–2. Even acknowledging that these references do not necessarily teach "maintaining or increasing cognitive development of a

foetal, infant, or child subject" as recited in the claims, we nevertheless agree with the Examiner that a person of ordinary skill in the art would understand that without "optimal neural development" and "[s]timulating the development of the nerve system" there can be no maintenance or increase in cognitive function, as the relationship between neural development and cognitive function is well known in the art. We are consequently not persuaded by Appellant's arguments.

Issue 3

Appellant argues that their evidence of surprising or unexpected results is sufficient to overcome the Examiner's *prima facie* conclusion of obviousness. App. Br. 16–17.

Analysis

Appellant points to the Schnaar Declaration, and to the Declaration of Angela Rowan, Angela Rowan (filed September 24, 2013) (the "Rowan Declaration") as supporting their contention that the presence of an unexpected property of gangliosides in the claimed compositions was unexpected. App. Br. 17.

Appellant points to the Rowan Declaration as opining that:

> As reported in the Application, an animal study using a complex milk lipid source of gangliosides demonstrated a significant improvement in rate of learning and exploring activity, and in bone density and body length in supplemented animals compared to controls when supplementation was extended beyond weaning. These results have been reported as Vickers M, Guan 3, Gustavsson M, et al[.,] Supplementation with a mixture of complex lipids derived from milk to

> growing rats results in improvements in parameters related to growth and cognition. Nutr. Res. 2009 29: 426-35.[4]
>
> These results were surprising because although gangliosides are recognized components of cell membranes in the brain, there have been no previous reports of gangliosides being orally active in cognitive development or in aspects of healthy growth, and there was no reason to expect that they would be orally active.

App. Br. 17 (quoting Rowan ¶¶ 72–73). Appellant therefore contends that both the identification of gangliosides as orally active in cognitive development and the discovery of the specific claimed amount of gangliosides that can activate this property are unexpected results. *Id.*

Appellant's Specification describes the performance of neonate rats (>22 days post weaning) fed on a diet of low 0.02% (low) to 1% (high) weight/bodyweight (w/w) gangliosides relative to measured food intake. Spec. ¶¶ 101–104, 107. Performance of the subjects in a Water Morris Maze test was then analyzed, and the results are presented in the Specification's Figure 1, reproduced below:

[4] We note here that Appellant's application on appeal, filed September 21, 2010, is a continuation of PCT/NZ08/00274, filed October 20, 2008. The Vickers reference is therefore not prior art with respect to the claims on appeal.

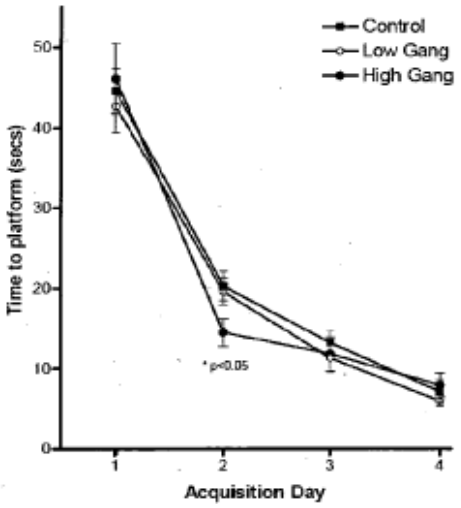

Figure 1 of Appellant's Specification demonstrates the performance of neonate rats fed high--ganglioside supplement low-ganglioside supplement, and control diets in the Morris Water Test

According to the Specification:

> There was an improved rate of learning and swim parameters of distance and speed on day 2 of the acquisition phase in High dose gel treated animals. But by day four there where [sic] no significant differences between the groups. The results indicated the High dose animals learnt the task faster than the control animals. The analysis indicates the animals did this by shorter swim distance and without swimming faster.

Spec. ¶ 110.

We are not persuaded. As an initial matter, Appellant relies upon the Schnaar and MacGibbon Declarations' opining that: "[N]one of the prior art suggests that orally administering gangliosides in any amount, let alone in an amount of at least 8 mg gangliosides per 100 g dry powder as claimed, would have any effect on cognitive development." Schnaar Decl. ¶ 67. We disagree. Fletcher and Beermann expressly teach that gangliosides are an important component of human breast milk, and Fletcher teaches that

gangliosides are important for optimal neural development, reasonably suggesting its use for cognitive development, as well.. *See* Fletcher 1–2; Beermann 2. Because human breast milk is perforce administered orally, we do not share the Declarant's surprise that increasing the level of ganglioside in a nutritional formula composition to a level approximating that of human breast milk would result in increased cognitive performance levels equivalent to that of children who were fed human breast milk. *See* Gurnida, *infra*.

Nor do we find the data from the studies adduced by Appellant to be probative of unexpected results. "To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). Appellant's Specification does not demonstrate that the control animals were fed a diet that was as high in phospholipids as those taught by either Shulman '790 or Shulman '091. Nor is it in evidence that the rats were fed compositions containing equivalent amount of gangliosides as those described in Fletcher.[5] Lacking such

[5] We here also note the rather obvious legal conclusion that Appellant's proposed unexpected results are not commensurate with the scope of the claims. Claim 32, for example, recites: "A method for maintaining or increasing cognitive development of a foetal, infant, or child subject…" with the clear implication that the subject is human. The Specification's subject test animals are weanling/pup Wistar rats, which cannot be reasonably construed as being infants or children. *See* Spec. ¶¶ 100, 104–105.

comparisons between the Example of the Specification and the teachings of the prior art, we are not persuaded that the results are unexpected. Thus, the results described in the Specification were not compared to the closest prior art.

Moreover, even were we, *arguendo*, to overlook the differences between the exemplary disclosure of the Specification and the teachings of the prior art, we are not persuaded that a small, but significant difference in the rate of learning at day 2 of the behavioral trials amounts to the requisite difference in kind, rather than degree, of difference sufficient to be persuasive of unexpected results. *See Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004) (holding that unexpected results that are probative of nonobviousness are those that are "different in kind and not merely in degree from the results of the prior art") (citation omitted). We consequently are not persuaded by Appellant that the disclosures of the Specification are probative of unexpected results.

Appellant also points ou that the Schnaar Declaration points to a prior art study published by D.A. Gurnida et al, *Association of Complex Lipids Containing Gangliosides with Cognitive Development of 6-month-old Infants*, 88(8) EARLY HUMAN DEV. 595-601 (2012) ("Gurnida"). App. Br. 17 (citing Schnaar Decl. ¶¶ 67–68; also citing Rowan Decl. ¶ 22). The Schnaar Declaration, in reference to Gurnida, states that, "none of the prior art suggests that orally administering gangliosides in any amount, let alone in an amount of at least 8 mg gangliosides per 100 g dry powder as claimed,

would have any effect on cognitive development." Schnaar Decl. ¶ 67 (quoting). The Schnaar Declaration opines that:

> The results are particularly surprising given that the control formulation contained gangliosides as well, just at a lower level. I would not have expected there to be such a significant effect on cognitive development associated with orally administering at least 8 mg gangliosides per 100 g dry powder, compared to administering 6 mg gangliosides.

Schnaar Decl. ¶ 68). Appellant therefore argues that both the identification of gangliosides as orally active in cognitive development and the discovery of the specific claimed amount of gangliosides that can activate this property are unexpected results. *Id.*

We do not find Appellant's arguments persuasive. Gurnida teaches a study comparing cognitive function in infants[6] fed on either: (1) standard infant formula (control); (2) standard infant formula "with added complex milk lipid to increase the ganglioside GD3 content by approximately 2–3 mg/100 g" (test group); or (3) infants who were breastfed (reference group). Gurnida 596. Of the compositions fed to the test and control groups, Gurnida teaches that: "Both study products were similar in composition (Table 1) except for increased arachidonic acid, phospholipid and ganglioside contents in the Complex Milk Lipid-supplemented [i.e., test group] formula." *Id.* With respect to the latter, Gurnida teaches that: "The complex milk lipid ingredient is a natural milk derived component that is acceptable for use in infant formula, and can be added at a level to give

[6] The test subjects were infants fed on the respective diets from 2–8 weeks of age until 24 weeks of age. Gurnida 596.

total ganglioside content within the range of ganglioside content in human breastmilk." *Id.* (emphasis added).

Gurnida teaches that:

> No significant difference was found between the control and treatment groups for the Griffith Locomotor, Personal–Social, and Hearing and Speech scores. However, there was a significant increase in scores for Hand and Eye Coordination and Performance and also for Total Score (General IQ) in the treatment group. Notably, all scores in this group were similar to those of the reference group (P>0.05; 2 sample t-test using both adjusted and unadjusted scores for the treatment group).

Gurnida 598. More specifically, with respect to the latter point, Gurnida teaches that: "Cognitive development scores and serum ganglioside levels for the treatment group did not differ from the reference group." *Id.* at Abstr.

To summarize, Gurnida teaches that infants fed with the phospholipid and ganglioside supplement performed significantly better on certain measures of cognitive development than did those fed on standard infant formula without supplement. Notably, there was no difference between the infants fed the supplemented composition and those fed on natural breast milk, which the supplement was expressly designed to mimic.

We do not find these results to be unexpected or surprising in view of the teachings of the prior art. Shulman '091 teaches that "it is an object of the present invention to provide a dietary supplement which guarantees the sufficient and recommended intake of phospholipids, in the form of a mimetic substitute of the phospholipids from human breast milk lipid, aimed especially for infants and young children consumption, as well as pregnant women." Shulman '091 5. Shulman '091 further teaches that:

> Some phospholipids, … are used as dietary supplements and a variety of health benefits are associated with their intake. These benefits include the improvement of cognitive functions, improvement of memory and concentration, maintenance of cellular membrane composition, and contribution to general well-being.
> …
> The dietary supplement of the invention are particularly intended for use in the enhancement of infants and/or children development, in the enhancement of infants and/or children cognitive development, in the enhancement of fetal development and in the enhancement of infants and/or children vision development.

Id. at 4, 16. Shulman '091 thus teaches that supplementing infant formula compositions with phospholipid concentrations approaching that of human breast milk could be expected to improve cognitive function.

Fletcher teaches that:

> [S]tandard infant formulas are typically produced using low-fat dairy products such as skim milk. Using a reduced-fat dairy product means undesirable components in milk fat are not included in the infant formula, but it also means that phospholipid and (glyco)sphingolipid levels are significantly lower than those in human milk.
>
> Research over the last 5–10 years has shown that increasing phospholipid and (glyco)sphingolipid levels in infant formulations to levels found in human milk (particularly ganglioside GM3, ganglioside GD3, ceramides and sphingomyelin) may lead to:… optimal neural development.

Fletcher 1–2. The combined cited prior art thus teaches that increasing the concentrations of phospholipids and gangliosides to approximate that found in human breast milk would provide increased neural and cognitive development compared to standard formula with lower concentrations of

those constituents. Gurnida validates these teachings of the prior art, demonstrating that supplementing formula with phospholipids and gangliosides to approximate the concentrations of those constituents found in human breast milk provides cognitive benefits that are equivalent to those derived from a diet of human breast milk. We conclude that a person of ordinary skill in the art, having comprehended the teachings of Shulman '091, Shulman '790, and Fletcher would have predicted the teachings of Gurnida. We further conclude that the teachings of Gurnida, and Appellant's Specification, are therefore not surprising or unexpected. We consequently affirm the Examiner's rejection of the claims.

CONCLUSION

The Examiner's rejection of claims 32–34, 45, 47–51, 53, 54, and 56–65 under 35 U.S.C. § 103 is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
32–34, 45, 47–51, 53, 54, 56–65	103	Shulman '790, Shulman '091, Fletcher, Beermann	32–34, 45, 47–51, 53, 54, 56–65	