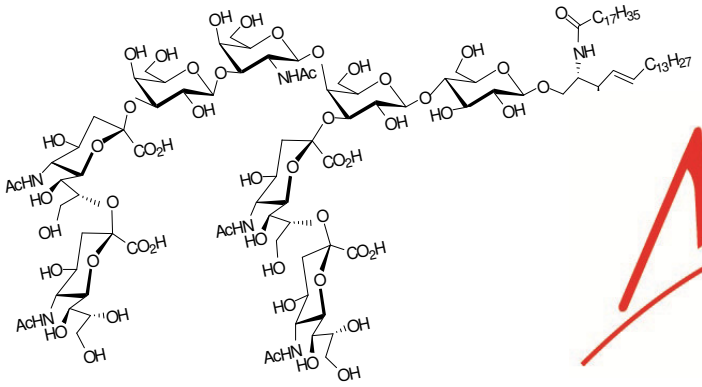


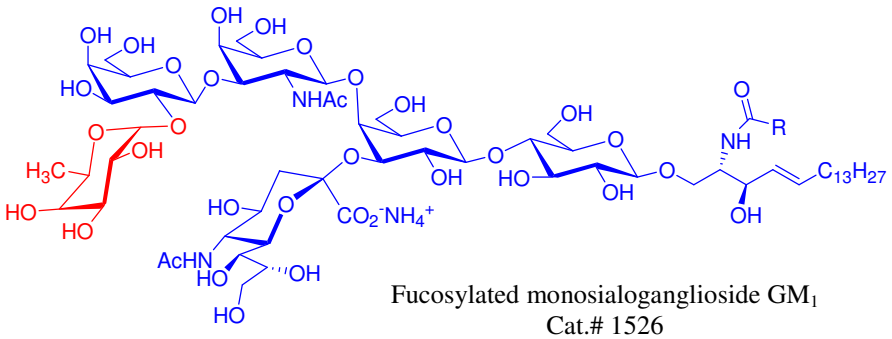
MATREYA LLC

Lipids and Biochemicals

NEWSLETTER FOR GLYCO/SPHINGOLIPID RESEARCH

AUGUST 2018

Fucosyl-GM1 is a Tumor-Associated Antigen



Fucosylated monosialoganglioside GM_1
Cat.# 1526

Fucosyl-GM_1 is a sphingolipid monosialoganglioside and tumor-associated antigen with a high prevalence in certain cancers while its expression is minimal in most normal tissue. A highly specific anti-fucosyl-GM_1 was found to bind to fucosyl-GM_1 on small cell lung cancer (SCLC) cells and activate antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and antibody-mediated phagocytosis. Dose-dependent antitumor activity was observed in a panel of SCLC xenograft models with tumor regressions occurring at doses greater than 0.3 mg/kg against tumors. Combination therapy of anti-fucosyl-GM_1 with standard of care chemotherapy resulted in significantly enhanced antitumor activity compared to monotherapy alone. Finally, studies conducted with this antibody in combination with anti-CD137 antibody resulted in significant improvement in efficacy.[(1)]

Hepatocellular carcinoma (HCC) is one of the most common human malignancies. Serum concentrations of anti-disialosyl galactosyl globoside (DSGG), anti-fucosyl-GM_1 and anti-Gb2 were significantly higher in patients with HCC than in chronic HBV infection individuals. Overall, the biomarker candidates DSGG, fucosyl-GM_1, and Gb2 of cancer-associated carbohydrate antigens achieved better predictive sensitivity than the current clinical biomarker serum a-fetoprotein.[(2)]

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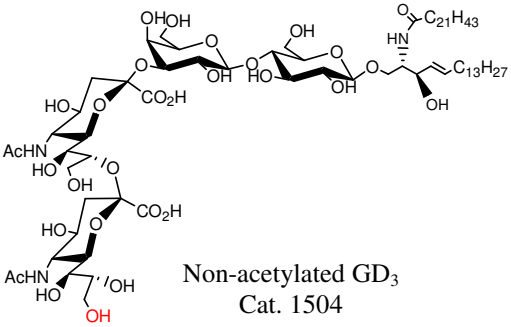
References:

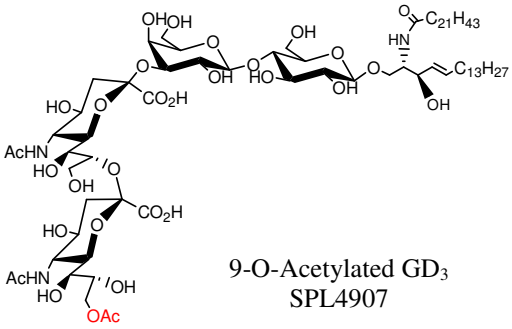
1. B. Chen et al. BMS-986012, a fully human anti-fucosyl-GM1 antibody has potent in vitro and in vivo antitumor activity in preclinical models of small cell lung cancer. [abstract]. In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; 2016 Apr 16-20; New Orleans, LA. Philadelphia (PA)

2. C. Wu et al. Cancer-associated carbohydrate antigens as potential biomarkers for hepatocellular carcinoma. *PLoS One*. 7(7), e39466 (2012)

O-Acetyl Gangliosides are Expressed in Tumor Cells



Non-acetylated GD_3
Cat. 1504



9-O-Acetylated GD_3
SPL4907

Gangliosides are sialic acid containing glycosphingolipids that play important roles in cell adhesion, cell recognition, signal transduction, and neural development. O-Acetylation of hydroxyl groups on the sialic acid is one of the most common modifications of gangliosides and can exist acetylated to the C-4, 7, 8 and 9 hydroxyl groups. This causes major changes in their physiological properties, resistance to sialidase hydrolysis, and lectin binding. Acetylated gangliosides have especially been correlated with various cancers.(1)

While an accumulation of the ganglioside GD_3 is known to induce apoptosis, acetylation to 9-O-acetyl-GD_3 renders it unable to trigger this important function. Because of this, there is a critical ratio between GD_3 and 9-O-acetyl GD_3 which promotes tumor survival in glioblastoma cell cultures. In glioblastoma cells, cleaving the acetyl group of 9-O-acetyl-GD_3 restores normal GD_3, resulting in a reduction in tumor cell viability while normal astrocytes remain unaffected.(2)

The O-acetylated-derivative of GD_2 has recently received attention as a novel antigen to target GD_2-positive cancers. The absence of O-acetyl-GD_2 expression on nerve fibers and the lack of allodynic properties of anti-GD_2 antibodies, which are believed to play a major role in mediating anti-GD_2 therapeutic antibodie's dose-limiting side effects, provide an important rationale for the clinical application of immunotherapeutic strategies in patients with O-acetyl-GD_2-expressing tumors.(3)

Expression of 9-O-acetyl GD_3 increases in Schwann cells (SC) following infection with *Mycobacterium leprae* (ML), the etiologic agent of leprosy. Immunoblockage of 9-O-acetyl GD_3 *in vitro* significantly reduces adhesion of ML to SC surfaces.(1)

Stability of 9-O-Acetyl Gangliosides:

9-O-Acetyl gangliosides readily revert to their non-acetylated form. They have a shelf-life of approximately 3 months when stored at -20°C. Long term storage of these compounds will result in a mixture of the acetylated and non-acetylated gangliosides. Therefore Matreya produces and purifies 9-O-acetyl gangliosides on a custom basis, to ensure the highest purity of the acetylated product. Please contact us for a free quote.

References:
1. V. Ribeiro-Resende et al. Involvement of 9-*O*-Acetyl GD3 Ganglioside in *Mycobacterium leprae* infection of Schwann Cells. *The Journal of Biological Chemistry.* 285, 34086-34096 (2010)
2. S. Birks et al. Targeting the GD3 acetylation pathway selectively induces apoptosis in glioblastoma. *Neuro Oncol.* 13(9), 950-60 (2011)
3. J. Fleurence et al. Targeting O-Acetyl-GD2 Ganglioside for Cancer Immunotherapy. *Journal of Immunology Research.* Article ID 5604891 (2017)

Product Name	Catalog #	Purity
9-O-Acetyl-monosialoganglioside GM_1	SPL4906	98+%
9-O-Acetyl-disialoganglioside GD_3	SPL4907	98+%

New Products from Matreya

- N-Hexanoyl-biotin-sulfatide cat. 2207
- N-Hexanoyl-biotin-disialoganglioside GD_3 cat. 2055
  - Biotin labeled lipids are useful for ELISA studies and for studying lipid/protein interactions

- *lyso*-Lactosylceramide, synthetic cat. 2088
- N-Octadecanoyl-sulfated-lactosylceramide cat. 1540
- N-Tetracosanoyl-D-*erythro*-dihydrosphingosine cat. 2093
  - Synthetic lipids are well defined standards for analysis and cellular studies

- N-(32-Linoleoyloxy-dotriacontanoyl)-sphingosine-**D9** cat. 2208
  - Omega-Esterified ceramides are vital components of the skin's water barrier. Stable isotope labeled standards are critical for analytical studies.

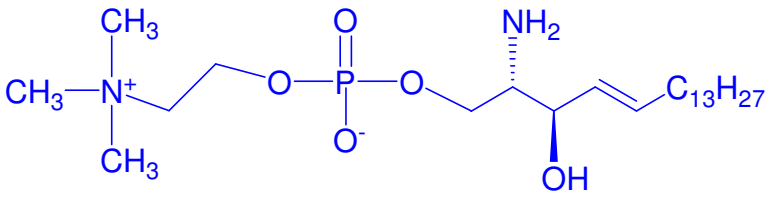
- N-Glycinated-glucosylsphingosine cat. 2089
- N-Glycinated lactosylsphingosine cat. 2090
- N-Glycinated *lyso*-sulfatide cat. 2092
  - Glycinated lyso-sphingolipids are highly useful as mass spectrometry internal standards with the glycine providing a unique mass without changing the important physical properties of the free amine.

- Methyl punicate cat. 1240
- Methyl jacarate cat. 1234
- Methyl stearidonate cat. 1277
  - Conjugated linolenic acids are found in very high amounts in various oils and exhibit some very powerful physiological effects.

- $^{13}C_6$-Glucosylsphingosine cat. 2209
- N-*omega*-CD_3-Octadecanoyl disialoganglioside GD_3 cat. 2054
- N-omega-CD_3-Octadecanoyl-phytosphingosine cat. 2210
  - Stable isotope labeled standards are critical for analytical studies.

- Sterculic acid cat. 1235
- Methyl sterculate cat. 1236
- Methyl malvalate cat. 1238
  - Cyclopropene fatty acids inhibit Δ9-desaturase and can cause carcinogenicity and acute and chronic toxicity.

lyso-Sphingomyelin as a Sensitive and Specific Biomarker for Niemann-Pick Disease



D-*erythro*-Sphingosylphosphorylcholine
Cat. 1318

Niemann-Pick disease is a lysosomal storage disorder that results in the accumulation of various lipids. Several biomarkers are currently used to diagnose and monitor this disease but none have proven to be ideal. *lyso*-Sphingomyelin (Sphingosylphosphorylcholine, *lyso*-SPM) has recently been identified as a highly sensitive and specific biomarker for Niemann-Pick disease.

Niemann–Pick disease type B (NPD-B) is caused by a partial deficiency of acid sphingomyelinase activity and results in the accumulation of lysosomal sphingomyelin (SPM), predominantly in macrophages. Notably, SPM is not significantly elevated in the plasma, whole blood, or urine of NPD-B patients. However, *lyso*-SPM is elevated approximately 5-fold in dried blood spots (DBS) from NPD-B patients and has no overlap with normal controls, making it a potentially useful biomarker.[1]

SPM levels have been shown to be significantly elevated in the livers and spleens of NPD-B patients while SPM levels in plasma have been found to overlap with those of normal controls. A recent LC/MS/MS analysis of dried blood spots showed that *lyso*-SPM levels from NPD-B patients were substantially elevated when compared to normal controls, with no overlap in values. *lyso*-SPM has the potential to be an NPD-B biomarker for diagnosis or disease monitoring.[1]

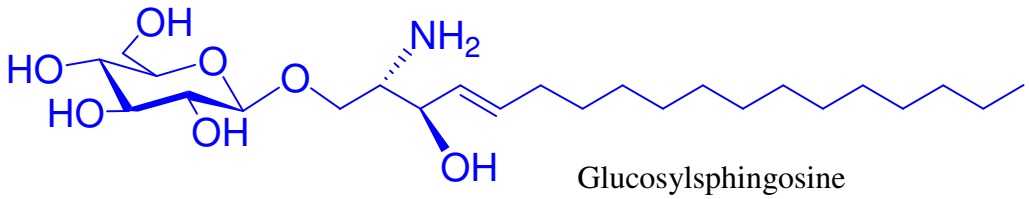
lyso-SPM has also been shown to be a precise and specific biomarker for Niemann-Pick Type C with a sensitivity of 100.0% and specificity of 91.0%. *lyso*-SPM analysis is relatively quick and easy to perform from blood plasma samples, making it useful in a clinical setting.[2]

References:
1. Wei-Lien Chuang et al. Lyso-sphingomyelin is elevated in dried blood spots of Niemann–Pick B patients. *Molecular Genetics and Metabolism* 111, 209-211 (2014)
2. Anne-Katrin Giese, A novel, highly sensitive and specific biomarker for Niemann-Pick type C1 disease. *Journal of Rare Diseases* 10:78 (2015)

Product Name	Catalog #	Amount	Purity
D-*erythro*-Sphingosylphosphorylcholine	1318	5 mg	98+%
L-*threo*-Sphingosylphosphorylcholine	1319	5 mg	98+%
Sphingosylphosphorylcholine (mixture of D-*erythro*/L-*threo*)	1321	10 mg	98+%
lyso-Dihydrosphingomyelin	1913	1 mg	98+%
N-1-13C-Hexadecanoyl-D-*erythro*-sphingosylphosphorylcholine	2200	1 mg	98+%

Please visit www.matreya.com for a full list of sphingomyelin products

Glucosylsphingosine as a Sensitive and Specific Biomarker for Gaucher Disease



Glucosylsphingosine

Lysosomal storage diseases (LSDs) are a heterogeneous group of disorders caused by lysosomal enzyme dysfunction.(1) Gaucher disease (GD) is the most common of these lysosomal storage disorders and has recently warranted much research due to the debilitating effects of excess lipid storage in Gaucher cells. A lack of activity in the lysosomal enzyme β-glucosidase, or occasionally in its activator protein saposin C, causes an accumulation of glucosylceramide, glucosylsphingosine, and other glycosphingolipids in macrophage cells, especially in the liver, spleen, lung, and bone marrow. These lipid heavy cells are commonly known as "Gaucher cells" and can result in hepatosplenomegaly, cytopenia, skeletal disfunctions, lung disorders, and neuronal degradation. In lipid storage disorders such as GD, it is very important to diagnose and treat patients as early as possible. One very effective method of diagnosis is the use of biomarkers.

Chitotriosidase is the most well-established biomarker for GD. However, it is not specific for GD and may give a false negative in a significant percentage of patients due to a particular mutation. Chitotriosidase also reflects the changes in the course of the disease belatedly. Furthermore, a significant percentage of the population, 6%, are deficient in the chitotriosidase gene.(2) Due to these limitations a more specific biomarker is needed for GD.

A recent report demonstrated that glucosylsphingosine can be used as a promising, reliable, and specific biomarker for GD and for measuring the effectiveness of enzyme replacement therapy. Evaluation of the sensitivity and specificity of glucosylsphingosine during enzyme replacement therapy showed significant decreased levels of glucosylsphingosine in both new patients and patients that had previously been treated. The quantitation of glucosylsphingosine was demonstrated to serve as a direct indicator of disease intensity and response to enzyme replacement therapy.(1)

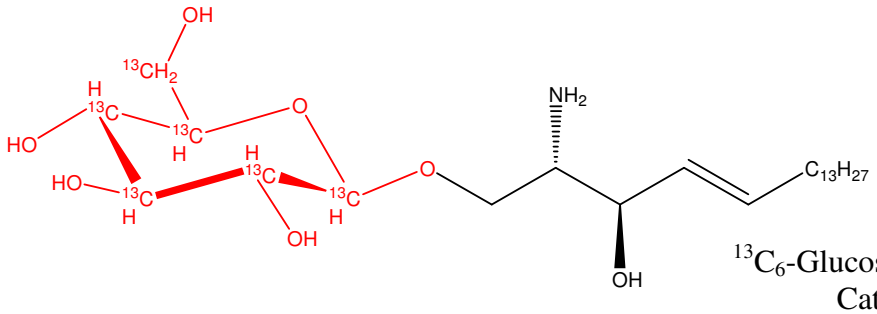
Taking advantage of glucosylsphingosine as a biomarker, M. Fuller et al.(3) have developed a quick and reproducible method for the determination of abnormally high glucosylsphingosine levels from 0.01 mL of plasma. The plasma is spiked with N-palmitoyl-d3-lactosylceramide as an internal standard, extracted with chloroform/methanol, and centrifuged to remove the insoluble protein precipitates. The sample is then ready to be analyzed by LC/ESI-MS/MS. Recovery of the glucosylsphingosine was found to be >90% as calculated from the quality control samples and the calibration curve was linear over the entire relevant range. The assay was described as "accurate, reproducible, robust, and easy to perform in routine laboratory settings". This method found that glucosylsphingosine was elevated in all GD patients compared to unaffected controls and patients with other metabolic disorders. These results have validated the effectiveness of glucosylsphingosine in diagnosing Gaucher disease and in monitoring the results of enzyme replacement therapy.

Matreya is pleased to now offer $^{13}C_6$-Glucosylsphingosine and N-glycinated

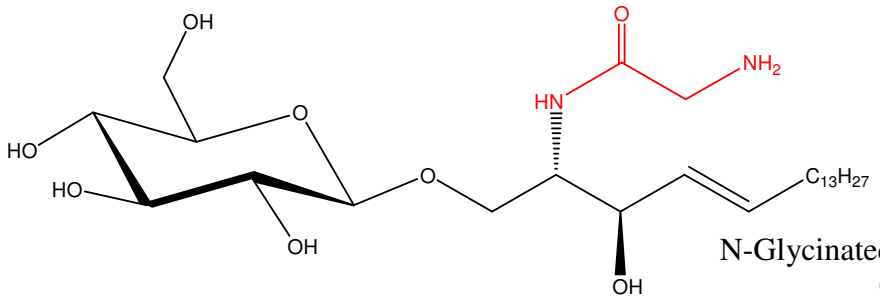
glucosylsphingosine as new, highly specific, glucosylsphingosine internal standards. 13C6-Glucosylsphingosine contains six carbon-13 units on the glucose moiety while N-Glycinated glucosylsphingosine contains a glycine attached to the amine of sphingosine, preserving its primary amine. These sphingolipids are ideal for use as internal standards in the extraction and mass spectrometry analysis of samples. The free amine group of glycine gives very similar physical characteristics to the natural sphingolipid while the glycine adds an additional 57 units to the molecule, making it easy to detect by mass spectroscopy methods.[4]

References:

1. D. Elstein et al., Reductions in glucosylsphingosine (lyso-Gb1) in treatment-naïve and previously treated patients receiving velaglucerase alfa for type 1 Gaucher disease: Data from phase 3 clinical trials. *Mol. Genet. Metab*. 122:1-2, 113-120 (2017)
2. R. Boot et al., The Human Chitotriosidase Gene NATURE OF INHERITED ENZYME DEFICIENCY. *J. Biol. Chem*. 273, 25680-25685 (1998)
3. M. Fuller et al., Rapid, single-phase extraction of glucosylsphingosine from plasma: A universal screening and monitoring tool. *Clinica Chimica Acta* 450, 6-10, (2015)
4. R. Krüger et al. Quantification of the Fabry marker lysoGb3 in human plasma by tandem mass spectrometry. *Journal of Chromatography B*. 883-884, 128-135 (2012)



$^{13}C_6$-Glucosylsphingosine
Cat. 2209



N-Glycinated glucosylsphingosine
Cat. 2089

Product Name	Catalog #	Amount	Purity
Glucosylsphingosine, synthetic	2086	5 mg	98+%
Glucosylsphingosine, buttermilk	1306	5 mg	98+%
Glucosylsphingosine, plant	1310	5 mg	98+%
$^{13}C_6$-Glucosylsphingosine	2209	1 mg	98+%
N-Glycinated glucosylsphingosine	2089	1 mg	98+%

Please visit www.matreya.com for a full list of glucosylceramide products