

Glyco-Forum section

A “Glyconutrient Sham”

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The discipline of glycobiology contributes to our understanding of human health and disease through research, most of which is published in peer-reviewed scientific journals. Recently, legitimate discoveries in glycobiology have been used as marketing tools to help sell plant extracts termed “glyconutrients.” The glyconutrient industry has a worldwide sales force of over half a million people and sells nearly half a billion dollars (USD) of products annually. Here we address the relationship between glyconutrients and glycobiology, and how glyconutrient claims may impact the public and our discipline.

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What are glyconutrients?

The journal *Glycobiology* serves the discipline of glycobiology by reporting studies “. . . about the biological significance of glycans . . .” in the broadest sense. *Glycobiology*’s contributors and readers include an international fellowship of investigators from academia and industry who devote their careers to probe glycan structure, metabolism, and function by developing and applying rigorous scientific tools and standards. Whether the goal is to understand the chemistry of carbohydrates, their metabolism, their biological functions, or delve into their commercial and biomedical potential, our community depends on exacting scientific standards coupled with honesty and accuracy in reporting results. The field of glycobiology has contributed insight into fundamental biological processes that have led to novel technologies and therapies that benefit mankind. With enhancements in synthetic, analytical, biochemical, and genetic tools, the field is poised to accelerate its rate of discovery.

Against this backdrop of rigorous scientific research, an industry has emerged for the sale of certain plant extracts that have been referred to as “glyconutrients.” The most financially

successful of these ventures is Mannatech, an international company based in Texas. A lawsuit filed last year by the Texas Attorney General⁵ accuses Mannatech (and affiliated organizations) of using “. . . false, misleading, or deceptive acts or practices . . .” to “. . . sell [glyconutrients] as a way to cure, mitigate, treat, or prevent diseases, illnesses or serious conditions, despite [their] admission that the products do not cure any disease, and despite the fact that this marketing violates both federal and state food and drug laws. . . .” People desperate for medical breakthroughs have spent billions of dollars to purchase plant polysaccharides whose medical value has not been subjected to FDA-approved clinical trials, or, in some instances, whose medical value has been disproved.

Mannatech describes “eight sugars” that they claim enhance health. At the Mannatech web site, they state:

Scientific research shows that eight glyconutrient sugars are needed at the cellular level for optimum wellness. They are: fucose, galactose, glucose, mannose, *N*-acetylgalactosamine, *N*-acetylglucosamine, *N*-acetylneuraminic acid, [and] xylose. You may not be receiving these beneficial sugars in the right amounts from the food you eat. That’s where Mannatech offers hope. Mannatech leads the industry in glyconutrient technology around the world and strives to offer better solutions for global health. (<http://www.mannatech.com>)

These particular 8 sugars are a partial list of the 10 most abundant monosaccharide components of vertebrate glycans (Werz et al. 2007). However, except for rare patients with certain types of congenital disorders of glycosylation (CDG) (Niehues et al. 1998), the inference that humans can benefit clinically from ingesting these monosaccharides is unsupported by controlled clinical trials. Furthermore, the relationship between Mannatech’s flagship product, Ambrotose[®] Complex, and vertebrate glycans is tenuous. Ambrotose[®] Complex consists of a mixture of partially purified polydisperse plant polysaccharides (see below). Claims of health benefits of ingesting Ambrotose[®] Complex, or its components, remain untested in controlled human trials, or have been disproved in such trials, depending on the indication. Despite this, according to the lawsuit, the glyconutrient industry and its salespeople infer that ingesting their products is required for “optimal health,” or cures disease. The public, with limited tools to judge these claims, is purchasing “glyconutrients” at a rate of >\$400 million per year from Mannatech alone.⁶

To the extent that the field of glycobiology is tied, in reality or perception, to what the Texas Attorney General alleges are “fictitious claims,”⁷ there is a risk that the field will be viewed with

¹The statements in this article are solely the opinions of the authors based on their reasonable evaluation of publicly available information.

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⁵<http://www.oag.state.tx.us/newspubs/releases/2007/070507mannatech.pdf>

⁶Mannatech press release, August 21, 2007; <http://www.secinfo.com/d14D5a.u5Mqf.d.htm>

⁷Attorney General of Texas press release July 5, 2007; <http://www.oag.state.tx.us/oagNews/release.php?print=1&id=2086>.

skepticism. More importantly, if discoveries from the field of glycobiology are misrepresented to convince seriously ill people to invest limited resources in unproven products, or to forgo standard of care (Attorney General of Texas press release July 5, 2007), we feel that there is a moral obligation for glycobiologists to speak out.

As part of their effort to build scientific credibility for their products, Mannatech notes their support of legitimate glycobiology conferences and asserts that glyconutrient supplements “are now recognized” in a prominent medical biochemistry textbook, *Harper’s Illustrated Biochemistry* (Murray et al. 2006). In addition, the Mannatech literature implies a link between the research of prominent glycobiologists and the health benefits of their glyconutrient products, despite the lack of convincing scientific bases for such claims. According to the Texas Attorney General’s lawsuit, three Nobel laureates have taken action to stop Mannatech from using their names to promote glyconutrient sales.

This commentary is intended to inform the glycobiology research community about the glyconutrient industry, using its largest company, Mannatech, as a case study. By understanding the basis of what the Texas Attorney General calls a “‘Glyconutrient’ Sham,” we hope to maintain a bright line between legitimate glycobiology research, including research into the potential of dietary glycans to be of health benefit, and what has become a vigorous marketing campaign to sell certain mixtures of plant polysaccharides as health products in the absence of controlled clinical studies to support their efficacy.

Mannatech history and business model

Mannatech was established in 1994 (Brammer 2005), the same year that the US Congress passed the “Dietary Supplement Health and Education Act” (Public Law 103-417). The law, in part, “. . . protects the right of access of consumers to safe dietary supplements . . . necessary in order to promote wellness,” dictating that dietary supplements (vitamins, minerals, herbs, extracts) are free from government regulation unless they are unsafe. This provided for the growth of the “nutraceutical” industry that provides dietary supplements, ranging from pure vitamins to crude plant extracts. Proof of a benefit to health is not required as long as a product is safe, labeled as a dietary supplement, and not marketed as a therapeutic.

The Mannatech business model includes multilevel marketing, in which “associates” (over half a million in 10 countries) (Mannatech press release, August 21, 2007; <http://www.secinfo.com/d14D5a.u5Mqf.d.htm>) are recruited to sell Mannatech products and to recruit additional associates. Associates are independent salespeople and not considered employees of Mannatech. Since sales contacts are often one to one between associates and prospective buyers, or via associate internet sites that are not directly managed by Mannatech, the company has distanced itself from unsupported therapeutic claims by associates. Mannatech’s web site states that “Our products help to build and maintain total health,” and add the footnote “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.” Nevertheless, the Texas Attorney General notes that associates tout Mannatech products to cure cancer, treat chronic diseases, and even reverse genetic disorders (such as Down syndrome). A recent Google search

of “Mannatech cancer” retrieved >60,000 hits, “Mannatech diabetes” >38,000 hits, and “Mannatech ‘Down syndrome’ ” >3,500 hits. These actual or implied therapeutic claims have raised questions, some of which have been brought to the attention of glycobiologists. Desperate patients or their loved ones (as well as physicians) have contacted the authors and their colleagues for advice on whether they should spend thousands of dollars to purchase glyconutrients to cure debilitating or fatal diseases. The authors have been able to find no clinical study in the PubMed database (National Library of Medicine) that supports the use of Mannatech’s flagship product, Ambrotose[®] Complex, for any clinical indication.

Glyconutrient products

Mannatech sells dozens of products, from children’s vitamins to skin creams. Many contain vitamins and minerals common to other multivitamin products. However, their flagship product, which is sold as a stand-alone product or as a distinguishing component in their other products, is “Ambrotose[®] Complex.” The company claims Ambrotose[®] Complex is the “first ‘complete’ glyconutritional supplement,” and according to their web site, millions of units have been sold worldwide.⁸

Ambrotose[®] Complex is reported by Mannatech to be a mixture of “arabinogalactan (*Larix decidua*) (gum), aloe vera (inner leaf gel powder), gum ghatti and gum tragacanth,” all of which are partially purified polydisperse plant polysaccharides. As dietary fibers, the components are considered largely indigestible. The first two have been explored as therapeutics whereas the latter two have been used widely as emulsifiers.

Larch bark (*Larix*) arabinogalactans consist of β -D-(1-3)-galactopyranan main chains with Gal- and arabinose-containing side chains extending from the 6-positions of the main chain sugars (Ponder and Richards 1997). Aloe vera inner leaf gel polysaccharide consists primarily of β 1-4-glucomannans with -4-mannopyranosyl- β 1- and -4-glucofuranosyl- β 1-residues in a ~15:1 ratio (Tai-Nin et al. 2005). Many of the mannose hydroxyl residues are acetylated (~0.8 acetyl groups per mannose), and a fraction of the mannose residues are 2-, 3-, or 6-substituted with galactose and/or other sugars. Gum ghatti and gum tragacanth are highly complex polydisperse branched polysaccharides consisting of galactose polymers with other saccharide constituents including arabinose, rhamnose, fucose, glucose, mannose, xylose, and uronic acids (Tischer, Iacomini, Gorin 2002; Tischer, Iacomini, Wagner, et al. 2002; Verbeken et al. 2003).

Two questions arise in considering whether Ambrotose[®] Complex is the “first ‘complete’ glyconutritional supplement.” First, humans (with the exception of certain rare CDG patients) biosynthesize the different monosaccharides the body needs from common dietary precursors, raising the question of whether dietary glycans are required for or significantly enhance glycosylation. Second, one must ask whether branched plant polysaccharides are effectively digested to provide biologically meaningful concentrations of individual monosaccharides that reach human tissues. While there are clearly established health benefits of including indigestible fiber in the diet, the implication that larch bark arabinogalactan, aloe vera gel glucomannan, and plant gum emulsifiers are a biologically significant

⁸<https://www.mannatech.com/Resources/en/us/pdf/FlagshipGlyconutrientSupplements.pdf>

source of dietary monosaccharides required for optimal cellular health appears to the authors to be unsupported. Nevertheless, the Texas Attorney General's lawsuit lists many instances in which Mannatech associates state that this particular mixture of plant polysaccharides is not only required for optimal health, but cures disease.

One marketing tool that some glyconutrient salespeople have used to infer the efficacy of glyconutrients is reference to Mannatech patents. Exemplary is US patent 6,929,807 (issued 2005, available at <http://www.google.com/patents>), which includes an impressive list of > 100 scientific references including published papers by distinguished glycobiologists, including those on the Editorial Board of *Glycobiology*. The patent includes a long list of disorders and diseases "... treated by administration of glyconutrients. ..." (alone or in combination with other nutraceuticals). The list of treated diseases, each listed with positive treatment results, is breathtaking: aging, stroke, multiple sclerosis, ALS, muscular dystrophy, cerebral palsy, macular degeneration, Down syndrome, immune deficiency, Tay-Sachs, Huntington's, Alzheimer's, Parkinson's, spinal cord injury, Crohn's, Tourette's, lupus, rheumatoid arthritis, alcoholism, atherosclerosis, asthma, allergy, silicon breast implant, agent orange, Gulf War syndrome, hepatitis, influenza, common cold, AIDS, cancer, and poor athletic performance (among others). Although the claims allowed by the patent office do not address the therapeutic efficacy of glyconutrients, the Texas Attorney General's lawsuit claims, "... Mannatech and its associates heavily rely on its ... patent for credibility and validation."

The awarded patent claims, protections offered by the US patent office (separate from the speculation allowed in the patent text), include "A dietary supplement composition, comprising: nutritionally effective amounts of isolated and purified galactose, glucose, mannose, *N*-acetylneuraminic acid, fucose, *N*-acetylgalactosamine, *N*-acetylglucosamine and xylose." The basis for determining "nutritionally effective amounts" of these monosaccharides in the absence of relevant data supporting their nutritional efficacy remains unclear. The matter appears to be academic, however, since polydisperse plant polysaccharides cannot be construed as "isolated and purified" monosaccharides.

Glyconutrient human trials

The "Dietary Supplement Health and Education Act" relieves nutraceutical companies from the requirement to perform human trials to support health claims of products. Blinded controlled human trials, the standard for FDA-approved drugs, are very expensive, and there is little motivation for nutraceutical companies to invest in them. On the other hand, the financial resources for investigators outside of companies to test nutraceutical claims are sparse. Given the financial pressures that limit clinical trials of nutraceutical claims, it is still worth considering the available published data that address potential health benefits of Ambrotose® Complex and its components.

A wealth of data connects glycans to human health and disease, and many valid publications support the conclusion that glycans are key components in human physiology. The relevant question for consideration of glyconutrients is: What is the relationship between the impressive body of biomedical glycobiology data in the peer-reviewed literature and the value to human health of ingesting glycans – particularly the plant polysaccha-

rides larch bark arabinogalactan, aloe vera glucomannan, and plant gums? As the accepted broad-based repository of published biomedical data, PubMed is a valid database in which to ask this question.

A search of PubMed for "Ambrotose" retrieved a single short editorial in *Harvard Women's Health Watch* that states, in part, "There's no good evidence to back any of these [therapeutic] claims" (Robb-Nicholson 2007). Breaking the search down to the components of Ambrotose®, a search of "(larch OR Larix) AND (arabinogalactan OR galactan)" returned 23 publications listed in PubMed in the past 25 years. Limiting consideration to papers reporting cellular, biochemical, physiological or therapeutic effects on humans, animals or their cells, and eliminating reviews and papers limited to testing arabinogalactan solely as a drug carrier, five papers in the past 25 years address the biomedical potential of larch arabinogalactan (LAG).

In vitro treatment of human cells and intraperitoneal injection in animals suggested that LAG stimulated natural killer (NK) cells (Hauer and Anderer 1993; Currier et al. 2003). However, a human trial indicated that ingested arabinogalactan "... is a non-digestible soluble dietary fiber that resists hydrolytic enzyme action and enters the large bowel intact ..." As dietary fiber, it was found to be well tolerated by healthy subjects and resulted in what was considered positive effects on the fecal flora (as does other dietary fiber), but did not change blood chemistry (Robinson et al. 2001). Two randomized double-blind trials of ingested LAG in healthy subjects demonstrated a lack of measurable effects. LAG administration for 4 weeks did not change immune cell counts, and there were "... no statistically significant pattern changes in the hematological or other immunological serum chemistry." No significant changes in subjective quality of life were found although 75% of those receiving LAG reported looser and more voluminous stools (Kim et al. 2002). In a separate 6-month study, healthy subjects ingesting LAG had no significant change in blood chemistries or gastrointestinal measures, except for a significant increase in flatulence (Marett and Slavin 2004). Taken together, one can conclude that LAG is generally a well-tolerated dietary fiber, without measured health benefits in normal subjects.

Aloe gel has long been reported to have medicinal value in treating burns and other skin lesions (Maenthaisong et al. 2007), whereas oral administration of aloe gel glucomannan is not as thoroughly studied. A PubMed search of "(aloe AND (glucomannan OR mannan)) OR acemannan OR Carrasyn" returned 56 published papers in the past 25 years ("acemannan" and "Carrasyn" are commercial names given to aloe glucomannan preparations). If one eliminates reviews and papers that address polymer structure only or that report the use of aloe extracts solely as wound or topical dressings, 30 papers remain. One of these papers reports a human clinical trial – the failure of oral aloe glucomannan to enhance immune system function or decrease viral load in AIDS patients (Montaner et al. 1996). The other 29 papers report a range of in vitro cellular and animal findings focusing primarily on immunostimulation and secondarily on treatment of viral infection or cancer using aloe glucomannan (for example, see Pugh et al. 2001). Notably, 20 of these 29 papers were co-authored by stakeholders of Mannatech or Carrington Laboratories (which supplies aloe glucomannan to Mannatech)⁹, or were funded by Carrington.

⁹<http://www.secinfo.com/ds8gj.u6.d.htm>

Although these data may warrant further investigation, from review of the biomedical literature represented in the PubMed database, there are no credible data supporting claims of health or therapeutic benefits from oral administration of aloe glucomannan in humans.

The emulsifier gums included in Ambrotose® Complex, gum ghatti and gum tragacanth, have not been the subject of any PubMed-indexed human clinical trials for any indication in the past 25 years. As accepted and broadly used food additives, exudate gums have been deemed nontoxic. In large quantities, gum tragacanth in healthy subjects was reported to act as indigestible dietary fiber, increasing fecal weight, but having no effect on clinical chemistry, hematology, or lipid metabolism (Eastwood et al. 1984). Taken together, we find no convincing support for human therapeutic or health claims of Ambrotose® Complex or its components.

Glycobiology is glycoscience

Glycoscience is synonymous with glycobiology (e.g. see <http://glycosciences.de>; <http://glycosciences.org.uk>). However, the URLs “<http://glycoscience.org>” and “<http://glycoscience.com>” point to the same Mannatech-maintained website.¹⁰ According to the Texas Attorney General’s lawsuit, the site “. . . purports to ‘provide information on nutritional saccharides – glyconutritionals – that form the scientific underpinnings for Mannatech’s product line . . .’” and was designed “. . . to give Mannatech’s products an air of legitimacy . . .” However, the lawsuit goes on to state that studies reported there “. . . have little, if any, scientific value.” According to the lawsuit, “. . . some of the studies referenced on the glycoscience.com website are legitimate studies that have been published in recognized journals. Those studies, however, are generic studies that have been done in the field of glycobiology and provide no support for the claims being made . . .” and furthermore, “. . . doctors in the field of glycobiology have strenuously objected to [Mannatech] using their work to mislead consumers into believing Mannatech’s products can cure diseases. Nevertheless, [Mannatech] continue[s] to encourage associates to use the studies in order to convince their non-medical . . . customers that Mannatech’s products have these incredible curative properties”. (See footnote 5).

The section of the web site devoted to “Glyconutritionals and Health” included illustrated narratives on glyconutritional implications in cancer, rheumatoid arthritis, asthma, inflammation, fibromyalgia and chronic fatigue syndrome, antimicrobial activity, recovery from viral infections, failure-to-thrive syndrome, cystic fibrosis, myasthenia gravis, and congenital muscular dystrophies. The linked articles contained descriptions of established findings from the disciplines of medicine and glycobiology, and speculation about the potential of glyconutrients to positively impact the disorders. Although glycobiologists can evaluate the admixture of scientific and marketing messages for themselves, the site was targeted to a nonexpert audience and was designed to appear as balanced scientific discourse.

Further obfuscating the “science” of glyconutrients is the “Fisher Institute for Medical Research,” a nonprofit research organization that lists among its goals “. . . to explore the extent,

if any, to which . . . glyconutritionals . . . provide integrative and complementary health and wellness support.” According to the Texas Attorney General’s lawsuit, the “. . . Fisher Institute is little more than a sham charity with the sole purpose of providing ‘scientific’ support to the illegal health claims made about Mannatech’s products.” The institute publishes the *Proceedings of the Fisher Institute for Medical Research*. According to the lawsuit and news reports (Robbins 2006), the directors of the Fisher Institute for Medical Research were major shareholders in Mannatech while managing the nonprofit. Despite an apparent conflict of interest, findings from the Fisher *Proceedings* have found their way into >1500 web references, including legitimate consumer health sites and reference lists in PubMed-indexed journals (Sierpina and Murray 2006).

Building glyconutrient credibility via glycobiology

Glycobiologists worldwide investigate the roles of glycans in human health and disease and publish their work in journals with exacting scientific standards. At the heart of this effort are carefully designed, unbiased investigations whose outcomes are evaluated dispassionately by expert referees before publication. Those who claim to speak for the glyconutrient industry often challenge the basic principles of scientific inquiry. Their unscientific dismissal of the principles of blinded clinical trials is at the heart of “testimonial reports” that tout nutraceuticals as therapeutics. At the end of these stories, the listener, reader or viewer is asked to decide whether adding “glyconutrients” to their diet will improve their health. The Texas Attorney General (See footnote 7) has characterized Mannatech as perpetuating “. . . illegal marketing schemes that prey upon the sick and unsuspecting,” and their marketing approach as an “. . . elaborate scheme to defraud innocent consumers . . .” Relevant to this marketing approach, the Texas Attorney General’s lawsuit also names Mannatech-associated “MannaRelief Ministries” as a codefendant, noting that the organization is a “. . . marketing tool . . . to promote Mannatech’s products” and “. . . perpetuate Mannatech’s illegal scheme.” Faith leads many to Mannatech, and that faith, combined with desperation and lack of tools to judge the claims of the company and its associates, can be a powerful basis for glyconutrient sales.

Given that the Texas Attorney General’s lawsuit accuses Mannatech of using “. . . false, misleading, or deceptive acts or practices . . .,” it is especially disturbing when the line between legitimate glycobiology research and glyconutrient sales becomes muddled. A “Technical Information” page entitled “Selecting the Ambrotose® That’s Right For You,” which is posted at the Mannatech-managed web site <http://glycoscience.org>, includes the statement, “Glyconutrient supplements are now recognized and defined in *Harper’s Illustrated Biochemistry*, a premier scientific textbook used in universities and medical schools worldwide”.¹¹ Although this appears to provide evidence that Ambrotose® is so well established as to be medical textbook material, the reference is to the insertion of glyconutrients into a chapter written by an academic who is also a Mannatech consultant (Sierpina and Murray 2006).

¹⁰<http://glycoscience.org> and <http://glycoscience.com> were recently shuttered, and at the time of this writing were “undergoing review,” reportedly in response to the Texas Attorney General’s lawsuit (Kaiser 2007).

¹¹ “. . . there is evidence that the other sugars may be beneficial in some circumstances when added to the diet. This has led to the development of glyconutrient supplements . . . The efficacy of such supplements is under study.” Murray et al. 2006, Chapter 46: Glycoproteins, p. 524.

Although the claim in the textbook that dietary sugars may be therapeutic "... in some circumstances ..." is carefully worded, and may be technically accurate (for example, mannose in the diet is therapeutic in the "circumstance" of rare cases of CDG), the broader implication of glyconutrient benefits is not supported by independent controlled studies. The inclusion of "glyconutrient supplements," by name, in a basic medical textbook provides a potential sales tool to build credibility and trust in products that have not been clinically proven.

Mannatech has also gained credibility through its support of legitimate glycobiology research conferences. For example, a summary of the *Proceedings of the 7th Jenner Glycobiology and Medicine Symposium* was published – without mention of Mannatech – in a volume of *Advances in Experimental Medicine and Biology* entitled "Glycobiology and Medicine" (Axford 2005). Essentially the same summary was published in the Mannatech marketing publication *Glycoscience & Nutrition* (Vol. 6, No. 3) with additional text added to note that the conference's "... major sponsor was Mannatech, Inc." Subsequently, John S. Axford, an academic glycobiologist who authored both articles (and was a Mannatech company director) stated that Mannatech "... had added a phrase stating that it was the 'major sponsor,' which was incorrect ..." (Kaiser 2007).

What can be done?

When the nutraceutical industry prepares and sells plant extracts as dietary supplements, it is of no special concern to glycobiologists. However, we feel that glycobiologists do have a responsibility to serve the public by speaking out against claims of glyconutrient therapeutic efficacy, often based on legitimate glycobiology discoveries, when there is a lack of credible clinical data to support such claims. This is especially important when those that the Texas Attorney General refers to as "the sick and unsuspecting," (Attorney General of Texas press release July 5, 2007; <http://www.oag.state.tx.us/oagNews/release.php?print=1&id=2086>) some of whom may need to choose between difficult therapeutic options, look to independent research scientists for clarity. As scientists, it is also our mandate to impress on the public the importance of rigorous unbiased studies to distinguish biomedical facts from marketing schemes.

Rigorous studies of the potential of saccharides to impact biology and medicine are an important and exciting part of our discipline. Furthermore, complementary and alternative medicine has a history of discovering therapeutics, and there is the potential for a strong link between such efforts and glycobiology. However, it is important that we distinguish rigorous research into complementary and alternative medicine from unsupported or poorly supported marketing claims. We can raise objections when inaccurate or misleading glyconutrient marketing materials appear in scientific journals or books. We can be vigilant for attempts to use legitimate glycobiology venues to enhance glyconutrient marketing. Finally, we can take advantage of questions raised by colleagues, academic and medical societies, funding agencies, the media, and the public as opportunities to discuss the compelling discoveries of glycobiology and distinguish them from marketing claims for polysaccharides that have not been subjected to appropriately controlled clinical trials.

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Conflict of interest statement

None declared.

Abbreviations

CDG, congenital disorders of glycosylation; LAG, larch arabinogalactan; NK, natural killer.

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