

# NATIONAL SHEEP INDUSTRY IMPROVEMENT CENTER

## Grant Application

Date Submitted	9-15-16	Legal Name of Applicant	Glycoscience Research Inc.
EIN	46-0448927		

Name Glycoscience Research Inc.

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County	Brookings	Congressional District	1st
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Project Title Comparison of meat composition of lambs affected with GM1 gangliosidosis to retail lamb

### Person to be contacted about application

Name	Susan Holler	Phone	605-695-9478	Email	sueholler@glycoscience research.com
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### Project Abstract (250-400 words) Include

#### Problem or Opportunity

Currently lambs affected with GM1 gangliosidosis are not allowed into USDA inspected harvest channels. When GM1 lambs are harvested at 4-6 months of age, in order to maximize the yield of GM1, neurological signs may be observed which prohibits them from entering inspected meat slaughter channels. The harvest of the GM1 for pharmaceutical use has been calculated to be profitable after harvest of tissues. However, the remaining carcass could be consumed if it can be verified to have the composition of meat utilized in inspected channels.

GM1 ganglioside is potentially a breakthrough treatment for people who suffer from Huntington's disease, a rare but fatal genetic neurologic disorder. Glycoscience Research Inc. has developed a natural source for GM1 ganglioside from genetically selected lambs that are homozygous for a single base mutation in the beta-galactosidase gene. Affected lambs accumulate 40 x levels of GM1 ganglioside in their tissues. These lambs represent the only viable source to produce this life saving chemical. Researchers and Pharmaceutical companies have tried to synthesize GM1 for the past 25 years, yet these lambs, according to Dr. Steven Hersch of Massachusetts General Hospital, a collaborator on the ovine GM1 ganglioside for HD project, represent the best hope HD patients have for a useful treatment. Currently, lambs are harvested at approximately 5 months of age, but since they display neurologic symptoms associated with the massive accumulation of GM1 ganglioside, they are deemed unsuitable for inclusion in the food chain. While the value of the carcass is minimal compared to its pharmaceutical value, we believe that if the meat is shown to be safe and wholesome, and equal to normal lamb, there will be no reason for exclusion from the human food chain if all other criteria for inclusion are met. GM1 ganglioside is a normal glycolipid component of the cell membranes of all mammals, and the safety of the molecule has been demonstrated in thousands of human patients when produced from bovine brain. While the diversion of a few research lambs is of little consequence, we anticipate that roughly 100,000 lambs will be needed yearly to treat HD, and when combined with the millions of lambs needed for Parkinson's disease and Alzheimer's disease, would represent a substantial and unnecessary production loss that can be returned to cooperator producers as well as provide an additional protein supply for consumers. This study is intended to establish the baseline chemical and nutritional attributes of GM1 lamb compared to normal lamb.



Avanti Polar Lipids Alabaster, AL	GM1 Ganglioside	\$300	10	\$3,000
<b>Overhead</b>		<b>Total Budget</b>		<b>Rate</b>
Indirect Cost	<a href="#">Click here to enter text.</a>	\$22,428	7.5%	\$1,682

**Provide a qualitative summary, or justification for budget expenditures: (200 word or less)**

Preparation and testing of samples from 20 lambs that are homozygous recessive for GM1 gangliosidosis and 20 lambs that have gone through inspected slaughter will be compared. Lab expenses are listed for muscle sample analysis. Glycoscience Research will provide matching funds for processing GM1 lambs \$100/lamb x 20 lambs = \$2000 match.

**Technical Objectives**

**Responsiveness to NSIIC Stated Priorities (from web site)**

GM1 ganglioside, a new and innovative sheep source product will greatly enhance profitability for sheep producers. At \$500 for each affected lamb destined for the pharmaceutical market, in addition to traditional sheep products. The meat from these lambs, once approved by USDA to go through inspected slaughter channels, will add additional value above the pharmaceutical value. Increased profitability for producers and additional markets for lambs will lead to expansion of sheep numbers. Many producers are interested in producing these lambs not only for the increased profitability but also for the humanitarian aspect for patients suffering from neurologic disease who are deficient in GM1.

**Prior USDA or other Federal Support**

In progress is a NSIIC funded grant: Development of ovine GM1 ganglioside for Huntington’s Disease. Additionally, an American Sheep Industry Let’s Grow grant: GM1 Sheep Production for Huntington’s Disease: Training Videos, Record Management and Cooperator Communications are in progress. The objectives of this proposal address a different aspect of the larger GM1 for HD project, not previously funded. There are many aspects to this project that will lead GM1 into the pharmaceutical market. With the addition of preliminary data from NSIIC funding, a SBIR proposal in collaboration with Dr. Steven Hersch, Massachusetts General Hospital is in preparation for submission to NIH-NINDS for a January 6 deadline.

**Identification and significance of the issue being addressed**

Allowing meat from GM1 lambs into the food chain will greatly increase available protein. Carcasses from these lambs represent a product that could be marketed at a reduced cost due to the increased return from the pharmaceutical product. The lower cost could compete with low cost imports. It is anticipated that approximately 400,000 total lambs, of which 100, 000 lambs will be destined for GM1 production, will need to be produced yearly to meet the pharmaceutical demand for GM1 ganglioside for a Huntington’s disease population of an estimated 30,000 clinical patients. Of these 400,000 half would be carriers and potential breeding stock while the remainder would be market lambs.

### **What are the goals to be achieved with this grant funding?**

As the research progresses showing the efficacy of GM1 in the pharmaceutical market, the meat from these lambs will contribute a substantial protein source for consumers. Currently, the small numbers needed for preclinical studies, does not represent a significant cost to production of GM1 ganglioside. As the number increases to a minimum of 100,000 lambs per year for HD, and increasing to millions as the Parkinson's community demands access to GM1, the waste of usable protein and lost potential revenue for producers will be significant. The comparison of these GM1 lambs to lambs that are currently consumed will provide the necessary data needed to allow these lambs into the food chain to increase the value of raising them.

### **Work Plan – Task, Methodology, Individual responsible, and location where work will be done.**

Preparation of samples, ash, fat, protein, and moisture content will be conducted at South Dakota State University in Dr. Keith Underwood's lab. SD Ag Labs, Brookings, SD will do sample handling, preparations and analysis for carbohydrates. Avanti Polar Lipids, Alabaster, AL will analyze samples for ganglioside Dr. Keith Underwood and Dr. Travis Hoffman will compile and analyze the data and summarize the results. Briefly, Lamb legs will be prepared for analysis by removing the bone, grinding, freezing in liquid nitrogen, and subsequently powdered using a commercial blender in order to produce a homogenous sample. In order to determine water or moisture content, approximately 5.5 g of sample will be weighed, placed in dry preweighed foil pans, covered in dried filter paper, and placed in an oven (Thelco Laboratory Oven) for 24 h at 100°C. After drying and reweighing, dried samples will be used to determine chemical fat content by extracting with petroleum ether in a side arm soxhlet (AOAC, 1990) for 60 h followed by drying at 100°C for 4 h. Chemical fat content will be calculated as the difference between dried and extracted sample weight. Crude protein will be determined by weighing approximately 200 mg of sample in nitrogen free foil sheets and inserting samples into a nitrogen analyzer (Rapid N III, Elementar, Hanau, Germany). Nitrogen content will then be multiplied by 6.25 to calculate protein contents of samples. Ash determination will be conducted to measure mineral content of muscle by placing approximately 3 g of sample in a preweighed crucible, dried for 24 h at 100°C to determine water content, ashed for 16 h at 500°C in a muffle furnace (Isotemp Programmable Muffle Furnace, Fischer Scientific, Waltham, MA). The remaining material represents inorganic or mineral content of samples.

### **Related Research or other efforts in this area of which you are aware, including an analysis of the competitive landscape if the award is for a commercial application.**

GM1 ganglioside is a natural membrane glycolipid, found in all mammals, with a complex structure composed of a sphingolipid backbone and a chain of sugars with a terminal galactose molecule. After the BSE outbreak, the unverified bovine GM1 was deemed a potential risk, and was eventually removed from pharmaceutical use. Synthetic methods have been tried, although the complex nature of the molecule has prevented success in any significant scale to date. Semi-synthetic molecules have also proved to be impossible to produce in any quantity. To date the ovine GM1 source is the only possible route for GM1 ganglioside production for pharmaceutical use. The lamb carcass is a by-product of GM1 ganglioside production and has a significant value if access to the human food chain is ultimately granted.

## Potential Post application in this area of development of research or commercial endeavor

Further development will be extensive. Once the preclinical data is collected a cascade of events and further research and application in clinical trials will occur, as producers manage these genetics to maximize GM1 production. The use of extensive electronic data will benefit producers as lambs are tracked from birth to harvest and into pharmaceutical processing. The project will include new infrastructure to harvest lambs and manufacturing to bring the product to market.

## Background and rationale (citation of publications if any)

Research on GM1 ganglioside has been ongoing for the past 50 years. The focus on GM1 ganglioside as a treatment for neurologic disease has continued to date, in spite of the fact that an approved source for the molecule is currently not available in the United States or other developed countries throughout the world. Ovine GM1 ganglioside is currently the only source that is plentiful and still meets the FDA requirement for source verification and traceability that can be expanded to meet a pharmaceutical need. The use of GM1 ganglioside for Huntington's disease based on ongoing research in animal models of HD sponsored by NSIC and The Shepherd's Gift confirms the utility and tremendous potential of this treatment. The impact for HD patients could be life changing. The impact on the US sheep industry could be transformative.

**Ganglioside GM1 induces phosphorylation of mutant huntingtin and restores normal motor behavior in Huntington disease mice.** Proceedings National Academy of Science Feb. 8, 2012, Vol 109, no 9 pp. 3528-3533. Alba Di Pardo, Vittorio Maglione, Melanie Alpaugh, Melanie Horkey, Randy S. Atwal, Jenny Sassone, Andrea Ciammola, Joan S. Steffan, Karim Fouad, Ray Truant, and Simonetta Sipione. (multicenter study)[www.pnas.org/cgi/doi/10.1073/pnas.1114502109](http://www.pnas.org/cgi/doi/10.1073/pnas.1114502109)

**A randomized, controlled, delayed start trial of GM1 ganglioside in treated Parkinson's disease patients.** Journal of Neurological Sciences. 2013. 324 p140-148. Jay S. Schneider, Stephen M. Gollomp, Stephanie Sendek, Amy Colcher, Franca Cambi, Wei Du. Thomas Jefferson University, Philadelphia, PA.

These publications represent the sentinel justification for development of GM1 ganglioside for treatment of HD and Parkinson's. The literature contains hundreds of publications on the potential benefit of GM1 in neurologic diseases.

## Relationship to industry, including technical, economic and social benefit

In addition to reversing the ongoing decline in US sheep numbers, GM1 has a significant humanitarian impact to treat a devastating disease. (HD) is an autosomal dominant genetic mutation in either copy of an individual's Huntingtin gene which results in a neuro-degenerative disorder that causes nerve cells in certain parts of the brain to waste away over a 10-20 year period. It affects muscle coordination and leads to cognitive decline and psychiatric problems. It typically becomes noticeable in mid-adult life, when most people are at the peak of their career. There is also a juvenile form that has a 5-10 year progression. Total annual direct care costs of HD in the US are about \$478 million. Another 1.9 billion each year is lost income as patients become unable to work.

## Cost benefit analysis

Benefit:Cost Analysis	Traditional		GM1 affecteds	
	lambs	revenue	lambs	revenue
Per 100 Ewes	180	\$35,100.00	135	\$26,325.00
180% lambing crop	180	\$35,100.00	135	\$26,325.00
wool production (lbs)	10	\$1,000.00	10	\$1,000.00
affecteds 25%			45	\$22,500.00
carcass value 90 lbs x \$2/lb			45	\$8,100.00
Total (gross)		\$36,100.00		\$57,925.00
Additional return				\$21,825.00
Less costs		\$30,000.00		\$30,000.00
Total (net)		\$6,100.00		\$27,925.00
Difference				458%

Benefit:Cost to Patients	
Disease modifying treatment for debilitating, fatal, neurologic disease	<b>PRICELESS</b>
US Annual direct care costs	478 Million
US Annual lost income (patient & care giver)	1.9 Billion
Annual est. projected revenue from drug	3-12 Billion

## Policy or decisions affected by results

The current policy of omitting all animals showing neurologic signs from inspected slaughter will hopefully be modified in the case of GM1 lambs. This neurologic condition is well documented in the scientific literature. Since GM1 ganglioside is a naturally occurring molecule in all mammals and has been shown to be safe even when administered in large quantities (Parkinson's study). The safety of the meat for human consumption should be realized and an exception made to allow these specific lambs into the food channel.

## Bio Sketch of each principal person

Keith Underwood, PhD: Meat Scientist in the Animal Science Department at South Dakota State University. Expert in fresh meat quality, composition, and meat animal growth. Keith received his Bachelor's Degree from Texas Tech University in Animal Sciences, and MS and PhD in Animal and Veterinary Sciences from the University of Wyoming with an emphasis in meat science focusing on fresh meat quality.

Travis Hoffman PhD: Sheep Extension Specialist for North Dakota and Minnesota, Assistant Professor at North Dakota State University. Travis received his Bachelor's Degree from South Dakota State University, MS and PhD from Colorado State University in Meat Science with an emphasis in lamb quality, value, and consumer perception. Hoffman has completed numerous applied research projects ranging from production management such as the Sheep Safety & Quality Assurance program to end product quality lamb focus with the 2015 National Lamb Quality Audit. Dr. Hoffman was employed as an instructor in Meat Science at South Dakota State University in 2015 to 2016. Travis was born and raised on a diversified sheep, cattle, and grain operation in northeast South Dakota. His family raises registered Corriedale sheep that have won numerous national honors. Dr. Hoffman's expertise in American lamb quality will provide insight in meat sciences portions of this study.

Larry Holler, DVM, PhD: Glycoscience Research, CEO, Diagnostic Pathologist and Animal Reproductive Disease Specialist in the Veterinary and Biomedical Sciences Department at South Dakota State University. DVM, Kansas State University, PhD, Washington State University, dissertation **Ectopic Neuritogenesis and Ganglioside Alterations in Ovine GM1 Gangliosidosis**. Expert in ovine GM1 ganglioside, maintained ovine GM1 gangliosidosis flock for 25 years.

Susan Holler, MS: Chief Operating Officer, Glycoscience Research Inc., B.S. in Animal Science and M.S. in Reproductive Physiology from Purdue University. She has been employed in research, teaching and diagnostic positions at University of Idaho, Washington State University, and South Dakota State University respectively.

**Financial Feasibility (i.e., Is the budget proportionate to the endeavor, and will the outcome have a financial benefit to the industry in the near term or will additional funding be required?)**

The budget will provide the data necessary for regulatory agencies to consider a special exemption to approve GM1 lambs into inspected meat channels. The addition of these lambs in the inspected food channel should provide added protein at a potentially reduced cost for the consumer, making lamb a more cost effective protein for the average consumer. This increased affordability should increase consumption of lamb and make lamb a meal that is cost comparable to other protein sources. With the substantial increase in lamb harvested, industry infrastructure has the potential to rebound to former levels.

**Business Soundness (i.e., Are project participants qualified and experienced)**

This collaborative project brings together scientists from two land grant universities. The meat science expertise is well represented by Drs. Underwood and Hoffman. Additionally Dr. Holler and Sue have had over 25 years of studying GM1 gangliosidosis and raising the lambs that produce this value added product.

**Management Ability (i.e., Are project participants qualified and experienced)**

Dr. Underwood and Dr. Hoffman have both specialized in meat science research, earning their PhD and continuing their careers in this area. Dr. Holler has a DVM and PhD and decades of studying the potential of GM1 to treat debilitating neurologic disease. He has collaborated with experts studying spinal cord injury, Parkinson's and Huntington's disease, who have realized the potential that these lambs provide for the pharmaceutical market. He was a collaborator on a pre-Investigational New Drug proposal that has been submitted and reviewed positively by the FDA. Additionally the Hollers have hands on experience in the day to day management of the flock (currently 500 ewes) for the past 25 years, providing knowledge on the feasibility of raising GM1 lambs.

**Potential Industry Impact (i.e., How can the industry be expected to benefit in both qualitative and quantitative measures?)**

The US sheep industry could benefit significantly in this unique value added sheep venture. Currently, 14 cooperators are producing GM1 lambs for a substantial premium for the preclinical stages of this project. The HD market will require a minimum of 100,000 GM1 lambs for an estimated 30 to 50 thousand patients who would receive treatment. HD is a fatal genetic disease. There is currently no treatment. Treatment will require a daily dose for life. It is anticipated that if we are successful with approval for HD, the need for further expansion to meet the need of Parkinson's patients will be almost immediate. There are approximately 1 million patients that suffer with Parkinson's disease. Current research is also very promising for Alzheimer's disease, an application with 5.4 million patients affected.

**Industry Support (i.e., What data or other information is available to substantiate industry's need or desire for this project?)**

This project was presented and offered to the Dakota Lamb Growers Co-op. There are 14 cooperating flocks incorporating over 5000 ewes. Several of these producers have had family members or have known families struggling with HD and are committed to producing lambs that could treat this devastating disease. With this initial group of producers the goal of producing 30,000 affected lambs to treat clinical HD patients can be reached in 10 years. A big concern is that once GM1 is approved in clinical trials the demand will be immediate and the supply of lambs needs to be present. Producers are now entering year 2 of the project, with the first groups of cooperator lambs currently being delivered. The industry has put an emphasis on reversing the current decline in sheep numbers. Just in the last 2 decades numbers have declined by nearly 7 million. GM1 has the potential to reverse this trend providing a new value added product for the industry, one that could not be imported.

**CERTIFICATION**

**To the best of my knowledge and belief, all data in this application is true and correct. The document has been duly authorized by the governing body of the Applicant and the Applicant will comply with all Grant requirement if the assistance is awarded.**

Signature S S  Date

**Name of authorized representative:**

Title

Email

Phone

Return this application to: [stevelee@nsiic.org](mailto:stevelee@nsiic.org)

If you prefer to send hard copies:

Steve Lee,  
Executive Director and Program Manager  
National Sheep Industry Improvement Center  
Box 646  
Rockland, Maine 04841  
207-236-6567

For FedEx or Other Delivery Services:

32 Gleason St

Thomaston, ME 04861

Download form to your computer, complete it and save it to your computer prior to submitting to the Sheep Center.

## Additional Information for Applicants:

### **Matching funds:**

In order to leverage funds available, NSIIC will assign 10 points to any application in which a match of cash or in-kind labor is contributed. In-kind matches may only account for 50% of the total match. Additionally, salaries or other expenditures that will be made by the applicant or the applicant's employer, irrespective of a potential grant award, cannot be used as a match.

A subtraction of 10 points will be made from the total score of any application that includes an overhead budget of more than 7.5% of the total grant request. Request for capital expenditures are discouraged, and may not exceed 20% of the total budget in any event. Please justify any requested funding for equipment or other capital expenditures.

**Notification to Applicants:** Applicants will be notified via e-mail that their application has been received within a day or two of receipt: After Review, all applicants will be sent a notice to the e-mail of the person listed as the contact person on the application. That notice will be one of three possible responses: 1) Your application did not score high enough for funding consideration 2) Your application scored high enough for funding as submitted 3) Your application scored high enough for funding but with modifications needed in the budget. You will be given the opportunity to make those modifications for funding or you may reject the modifications in which case the grant funding offer will be withdrawn. Instruction will be included in the notice. Please note that the Review Committee will not provide feedback to applicants however in some cases the Board may elect to encourage re submission with certain specific changes (i.e. those the Board feels were good causes but poor application preparation or those with a good idea but not sustainable as presented). In some instances the Board may want to provide a written statement, with the understanding that no further discussion is available. Please note that proposals submitted more than twice will not be evaluated. The NSIIC Board request that applicants refrain from communicating with Board Members specifically about the project (i.e. Lobbying your project). Under no circumstances will applications arriving past the deadline for submission be considered