Pages 1 through 139 redacted for the following reasons:

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The University of Oklahoma®

OFFICE OF TECHNOLOGY DEVELOPMENT

Resubmission of U.S. Manufacturing Waiver Request

Submitted to:
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Invention Report Number:	1524003-01-0018 1524003-02-0010 1524003-01-0013 1524003-01-0014
Grantee/Contractor Org:	1524003 University of Oklahoma Health Sciences Center
Grant/Contract Number:	GM035978; NSF 9876193
Invention Title:	Group C Hyaluronan Gene and Uses Thereof DNA Encoding Hyaluronan Sythase from Pasturella Multicida and Methods of Use Streptococcus Equisimilis Hyaluronan Synthase Gene and Expression Thereof in Bacillus Subtilis Novel Kinetic Properties of Hyaluronic Synthases
Invention Docket Number:	97HSC020 98HSC027 98HSC027-1 02HSC045
Patent Docket Number:	See Attachment 1

July 27, 2010

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RE: U.S. Manufacturing Waiver Request for Invention Report Numbers: 1524003-01-0010; 1524003-01-0013; 1524003-01-0014; 1524003-01-0018; 1524003-01-0013

The University of Oklahoma (the "University") submitted a request for a Waiver of the Preference for United States Industry for Invention Report #1524003-01-0013 on or about October 27, 2009 ("Waiver Request"), which was granted, in part, pursuant to a April 22, 2010 letter from John Salzman (the "Waiver"). The purpose of this letter is to seek clarification and reconsideration of the scope and conditions of the Waiver.

I. Background

As set forth in more detail in the Waiver Request, the University, with funding from the National Institutes of Health and the National Science Foundation ("Funding Agencies"), developed technology for the recombinant production of hyaluronic acid ("rHA"), and subsequently licensed the technology to Hyalose, LLC, a company formed in Oklahoma, in 2000. After considerable effort, Hyalose, LLC was unable to identify or attract any companies that were willing to sublicense the rHA technology and develop full-scale production capabilities for rHA in the United States. See Waiver Request, Sec. III.B. Later, Novozymes A/S ("Novozymes") entered the hyaluronic acid business and approached Hyalose, LLC about a potential sublicense for the rHA technology. In May 2002, Hyalose, LLC granted Novozymes A/S ("Novozymes") an exclusive license to practice the rHA technology.

The University submitted its Waiver Request after multiple feasibility analyses by Novozymes revealed that it would be cost-prohibitive to manufacture rHA in the United States ("U.S."). The Waiver recognizes and accepts that it is not commercially feasible to manufacture rHA in the United States and, thus, waived the requirement to substantially manufacture rHA in the United States.

The Waiver, however, contains limitations and conditions that will prevent the commercialization of the rHA technology, which will deprive the public of the substantial benefits of rHA as described more fully in the Waiver Request. See Waiver Request, Sec. II. First, the Waiver does not include all applicable inventions, which is the result of the University's inadvertent failure to identify all inventions relevant to, and a part of, the rHA Technology in the Waiver Request. Second, the Waiver restricts manufacturing options outside the United States to Denmark. Unfortunately, as detailed in the Waiver Request, it is not commercially feasible to manufacture rHA in Denmark. In particular, among other things, given the significant employer costs attendant to manufacturing in Western Europe, manufacturing in countries such as Denmark simply is not feasible; indeed, production testing for rHA at Novozymes' Danish facilities has shown a "significant net operating loss." See Waiver Request, Sec. IV.A. The University requests, for the reasons stated below, that if the Waiver must be limited to specific locations, that the Waiver at least include Bulgaria and China, which appear to provide the best chance for economically-feasible manufacturing. Finally, the Waiver is limited to three years, which creates an insurmountable risk from a business perspective that production may not be able to continue after the expiration of the three-year Waiver. As described in Section IV below, the University requests that the Funding Agencies with iEdison

modify the three-year limitation to apply only to requests for additional or different manufacturing locations.

In an attempt to rectify the above-mentioned issues, the University respectfully requests that the Waiver be modified as set forth below. For the sake of brevity and clarity, this letter will refer to specific sections of the Waiver Request and hereby incorporates by reference the relevant background information therein.

II. Additional Relevant Inventions

As stated above, the Waiver Request inadvertently failed to include reference to all inventions relevant to the rHA Technology for which the University is seeking a manufacturing waiver. Please see Attachment 1 for all applicable inventions and invention report numbers. The University respectfully requests that the agency expand the scope of the Waiver to include all such inventions. The additional inventions are an integral part of the rHA technology and, thus, expanding the waiver to include these inventions is necessary. Further, expanding the waiver to include the additional invention records will not increase the technology or products being manufactured outside the United States because the additional inventions merely are components of the rHA technology.

III. Manufacturing Locations

As explained more fully in the Waiver Request, and accepted in the Waiver, the benefits of the rHA technology will not be realized if the rHA is required to be manufactured in the U.S. because current U.S. facilities lack the capacity for rHA manufacturing and domestic manufacturing would be cost-prohibitive. More directly, as stated in the Waiver, "[n]o facility in the United States suited for B. subtilis appears able to do the extraction, and retrofitting a plant while meeting cGMP requirements would be cost-prohibitive (building a new plant would be even worse)." See Waiver, pg. 1.

The Waiver, however, appears to limit the options for foreign manufacturing to Novozymes' existing facilities in Denmark, which was not the intent of the Waiver Request, and if not amended per this letter would not make it feasible for Novozymes to provide the benefits of this technology to the U.S. market. Specifically, the Waiver states that "Novozymes can cost-effectively adapt a food-grade facility in Denmark to manufacture the products and meet cGMP requirements" and that the Waiver therefore is limited to the "use of the licensee's [Novozymes'] existing facilities only as discussed in the waiver request." See Waiver, pgs. 1-2. The Waiver Request did not state this use of a Danish facility for full-scale production. To the contrary, as noted above and as explicitly stated in the Waiver Request, the tests run at Novozymes Denmark facility to determine feasibility revealed that permanent, full-capacity production of rHA at Novozymes' existing facilities in Denmark would be cost-prohibitive. See Waiver Request, Sec. IV.A. Indeed, the limited production test run at the Denmark facilities resulted in a "significant net operating loss." *See id.*

The Waiver Request suggested, based on thorough analyses, that full-scale production in China at an existing Novozymes site likely is economically feasible due to lower capital and labor costs, and that economically and commercially feasible options outside China may exist as well. See Waiver Request, Sec. V. Simply put, the Waiver Request sought a waiver of the domestic manufacturing requirement to allow rHA production by the University's licensee and sublicensees at one or more facilities in China and other potential foreign locations that prove to be economically feasible. Such a waiver would provide the greatest opportunity for successful production and commercialization of the rHA Technology.

The University, Hyalose, and Novozymes believe a license without geographic restrictions is the only feasible way for the benefits of the rHA technology to reach the U.S. market and, therefore, request that the Funding Agencies grant a revised waiver without identifying a specific location outside the U.S. for manufacturing. If, however, the Funding Agencies are required to identify specific locations for manufacturing outside the U.S., the University and Novozymes request that the Funding Agencies at least approve China and Bulgaria as permissible manufacturing locations for Novozymes and its sublicensee.

A. China

As explained in more detail in the Waiver Request, the business model run for this specific case suggests that manufacturing in China would allow for financially viable commercial production due to lower capital and labor costs. See Waiver Request, Sec. V. Novozymes has conducted the economic due diligence related to a rHA production facility for non-occupied land in Tianjin, China with existing infrastructure, waste water treatment and basic utilities in place. Investment in a new facility on this site in Tianjin is estimated to be approximately (b)(4) the cost for a U.S. facility. Combined with the lower labor costs, the overall business case for China is positive with a reasonable margin for downside risks such as delays and price erosion. Moreover, reduced production costs will prevent significant product price increases for the consumer. The facility in China will be designed for the production of pharmaceutical grade rHA and will not be constructed to include cosmetic grade manufacturing.

B. Bulgaria

Since the submission of the Waiver Request an additional analysis was conducted by Novozymes' sublicensee identifying Bulgaria as an economically viable manufacturing location due to the identification of a contract manufacturer with existing facilities potentially capable of supporting the full manufacturing process for cosmetic-grade rHA (fermentation → recovery/purification → spray drying) with relatively minor modification and investment. Under the contractual arrangement with Novozymes' sublicensee, Novozymes will not be producing cosmetic grade for its sublicense. As stated in the Waiver Request, the entire production process for rHA must be completed as one continuous process in the same plant because the liquid concentrate is not microbially stable during longer storage time and extended time between steps may result in product degradation. The lack of existing facilities with the capacity and capability of manufacturing with little to no additional capital investment has been the primary roadblock to full-scale commercial manufacturing to this point. Without the need for significant initial capital expenditure, cost estimations for manufacturing in Bulgaria at approximately (b)(4) per kilogram indicate a viable business case for commercial manufacturing. Simply put, the option of manufacturing cosmetic-grade rHA in Bulgaria is needed to bring the rHA technology to the United States.

IV. Waiver Duration

Finally, the Waiver is limited to a three-year period starting from the date of the Waiver. To the extent the entities did so, the University and Novozymes did not intend to imply that such a limited waiver would alleviate the financial roadblocks to full-scale production. Full-scale production in China, Bulgaria, or any other foreign location, will require expenditures that cannot be justified based on a waiver limited to three years. In other words, Novozymes or its sublicensee could not justify, from an economic standpoint, planning, modifying and/or building and staffing a rHA manufacturing facility based on a three-year waiver. The University requests a waiver without restrictions to duration, which would provide the most options and best opportunity for expedient, cost-effective commercialization by Novozymes and its sublicensee. That being said, the University and Novozymes recognize that the three-year limitation likely satisfies a Funding Agency and iEdison preference in waiver approval and oversight. As such, if the Funding Agencies and iEdison cannot grant a perpetual waiver for this technology, the University requests that the Funding Agencies and iEdison remove the three-year limitation and replace it with a requirement that Novozymes and its sublicensee must reapply for a waiver if Novozymes desires, anytime after three years from the date of the waiver, to relocate or expand the manufacturing facilities. This will allow the manufacturer some level of comfort that it might at least be able to recoup its capital costs with respect to manufacturing facilities built within the three year waiver period.

V. Conclusion

Novozymes has made considerable effort in attempting to commercialize the rHA technology and bring the benefits of the technology to the U.S. and international markets. Based on these efforts, as well as the initial efforts by Hyalose, LLC to identify a licensee, it is clear that not only is manufacturing

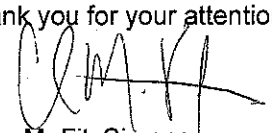
substantially in the U.S. cost-prohibitive, but that the options identified in this request are the only options for full-scale manufacturing and bringing this technology to the public.

Moreover, as stated in Section II of the Waiver Request, there are numerous benefits to the U.S. from bringing this technology to market in a cost-efficient manner, including, but not limited to, improvements in safety and quality of important medical products and cosmetics, generation of revenue through license fees, and the job creation associated with bringing a new product to market in the U.S., where jobs will be created both at Novozymes and at companies who will make products that then become feasible because of rHA production.

For all of the above reasons, the University of Oklahoma submits and hereby requests, jointly with Novozymes and Hyalose, LLC, modification of the Waiver to allow rHA production by the University's licensee and sublicensees in one or more foreign locations, and for the duration to be altered such that the necessary capital requirements to build a facility in a foreign country can be justified.

Please let us know if you require any other information in support of the request, or if you would like to discuss this matter.

Thank you for your attention to this matter. We look forward to hearing from you.



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ATTACHMENT 1

iEdison Reporting Entry/Tracking

97HSC020 Federal funding was not indicated in Disclosure document **1524003-01-0018**
All patents include the Federal funding statement referencing NIH GM035978
35541.003
35541.004
35541.069
35541.099
35541.105
35541.112
35541.117
35541.108
35541.110
35541.064
35541.100
35541.104
35541.109
133541.114
35541.102
35541.005
35541.006
35541.007
35541.073
35541.002
35541.011
35541.063
35541.103

98HSC027 Federal funding was not indicated in Disclosure document **1524003-02-0010**
All patents include the Federal funding statement referencing NSF 9876193
35541.025 (35541.026wo PCT)
35541.081
35541.101
35542.116

98HSC027-1 No Disclosure document **1524003-01-0013**

All patents include the Federal funding statement referencing NIH GM035978

35541.048 (35541.078wo PCT)

- 35541.098
  - 35541.111
    - 35541.115
      - 35541.119

35541.049

- 35541.102

35541.010 (35541.009wo PCT)

- 35541.011
  - 35541.063
    - 35541.103

02HSC045 Disclosure document indicates NIH GM035978 funding **1524003-01-0014**

All patents include the Federal funding statement referencing NIH GM035978

35541.062

35541.082 (35541.084wo PCT)

- 35541.107

October 27, 2009

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RE: U.S. Manufacturing Waiver Request for Invention Report Number: 1524003-01-0013

I. Introduction

The University of Oklahoma, with funding from the NIH, developed technology for the recombinant production of hyaluronic acid ("rHA"), and subsequently licensed the technology to Hyalose, LLC, a company based in Texas, in 2000. In June 2001, Hyalose, LLC entered into an exclusive option and license agreement with Novozymes A/S ("Novozymes") for the rHA technology.

Novozymes, Hyalose, LLC, and The University of Oklahoma subsequently conducted a joint research project, with funding from Novozymes, aimed at demonstrating the potential for commercial production using the technology. Due in part to the success in meeting early project milestones, Novozymes exercised its option for an exclusive license to the rHA technology in May 2002.

Subsequent feasibility analyses to assess commercialization options for rHA, however, have revealed and led to the conclusion that it is not financially feasible to manufacture rHA in the United States ("U.S.") due to prohibitive costs and lack of consistent production capacity resulting from inadequate equipment. For the reasons provided in this letter, the University of Oklahoma submits, and jointly with Novozymes and Hyalose hereby requests a waiver of the substantially manufactured clause.

II. Significance of rHA

HA is a key ingredient in a large number of medical and cosmetic applications and products. Technical cosmetic applications include high-end care topical moisturizers, high-end suntan lotions, an ingredient in nutraceuticals, and an injectable wrinkle remover and lip augmenter. Some key medical applications of HA include intra-articular injections for osteoarthritis, prevention of post-operative adhesions, intra-ocular surgeries and dermal fillers for cosmetic surgery and urinary incontinence. U.S. companies hold a market leading position in these market segments based on their innovative HA-based products. Examples are listed below:

US-based Companies	Application	Leading Brand
Genzyme	Intra-articular injections for treatment of osteoarthritis	Synvisc
Genzyme	Prevention of post-operative adhesions	Sepra
Alcon / Abbott	Intra-ocular surgeries	Viscoat / Healon
Allergan	Dermal fillers for cosmetic surgery	Juvederm / Hylaform / Captique

Because of its multiple and frequently used applications, HA is one of the most used biomaterials for medical devices in the U.S., and as depicted in the table below, these procedures touch millions of U.S. patients each year, and generate significant income for U.S. based companies:

Indication area	U.S. procedures 2008	U.S. sales 2008 (in millions)
Intra-articular injections for osteoarthritis	3,960,000	535
Prevention of post-operative adhesions	990,000	154
Intra-ocular surgeries	4,370,000	218
Dermal fillers for cosmetic surgery	1,924,000	399
Total	11,244,000	1,306

Source: Market research reports[i].

Benefits of recombinant HA technology

The rHA technology has the potential to deliver a number of important benefits to U.S. patients using HA-based products, as well as U.S. companies sourcing HA for medical applications. Indeed, the technology recently received the golden innovation award during the 2008 Congress on Pharmaceutical Ingredients and Intermediates (CPHI) in recognition of its potential to improve HA sourcing, and also has been referenced in several journals as an important milestone in the development of a high quality HA production system for medical applications.[ii]

Prior to the discovery of the rHA manufacturing technology, there were only two production methods for HA, both of which come with inherent problems that can potentially result in significant quality and safety related issues for patients using HA products, and for companies sourcing HA. This recombinant production technology for HA addresses many of the problems inherent in existing production methods and sets a new benchmark for the manufacture of an important medical ingredient that has been used in the U.S. medical industry for several decades.

The first generation of HA production technology, which is slowly being phased out, is based on extraction of HA from the combs of specially bred roosters. The rooster combs have a high concentration of HA, which has traditionally been extracted in a process involving use of chloroform and multiple organic solvents.

The resulting material has been very expensive to manufacture and given the animal-derived source, there is a potential risk for viral contamination and the presence of avian contaminants that may elicit an immunogenic response[iii]. Several of the marketed products based on avian sourcing thus carry a warning label regarding avian allergies. Examples of major products still using avian sourced material in the U.S. are listed below:

U.S.-based Companies	Indication area	Leading Brand
Genzyme	Intra-articular injections for treatment of osteoarthritis	Synvisc
Alcon / Abbott	Intra-ocular surgeries	Viscoat / Healon
Allergan	Dermal fillers for cosmetic surgery	Hylaform

A second generation technology for HA production was developed to deal with the issue of avian based production. This technology used the pathogenic bacteria *Streptococcus equisimilis* and *zooepidermicus*. Both of these bacteria have a capsule of HA surrounding them, which they use to evade the immune system of both humans and animals during infection[iv].

The use of *Streptococcus* has largely removed the concern regarding an animal extracted source, but has left other issues of concern. In particular, the pathogenic nature of these organisms presents a risk in terms of the potential presence of hemolytic toxins and antigenic proteins. However, manufacture of HA with these strains often requires the use of complex media that contain animal derived components, and close control of the molecular weight of the produced HA polymer is not easily achieved.[v]

The rHA technology is a new source for HA production designed to address the needs for increased purity of HA, as well as an interest in tighter process control that can yield more defined HA polymers in terms of molecular weight[vi]. In particular, a recombinant HA process results in:

- ***Higher purity HA***. The recombinant process is documented to be completely non-animal and thus free of any concerns associated with viral contaminants from animal sourcing. The strain (*Bacillus subtilis*) is non-pathogenic and does not produce any endotoxins or exotoxins, and is used for production of several GRAS (Generally Regarded As Safe) products already approved by the FDA. Furthermore, the purification process employed does not use any organic solvents and is capable of delivering a significantly purer HA product when compared to competing sources of HA. This should translate into purer HA products that will result in fewer potential adverse events for patients, and a greater confidence by U.S. companies in applying HA for applications that require a high degree of control with respect to product purity. Today, there is a strong focus among U.S. companies and the FDA on the presence of endotoxins and antigenic proteins present in some HA sources. In fact, some biomedical companies are pushing, along with the FDA, for tighter controls on these contaminants, which Novozymes believes will be substantially accomplished with the new rHA technology.[vii] The rHA technology makes higher purity HA.

- ***Increased consistency***. Another major issue is that the first and second generation production systems for HA do not yield a reproducible product in terms of the molecular weight of the polymer. This has significant implications for companies working with HA, particularly with large volumes of HA, as it makes it exceedingly difficult to control both the functionality of the final product that is related to the molecular properties and the processing of HA into its final form for medical applications. Many of the U.S. companies Novozymes has spoken with have expressed a very strong need for improved consistency in current sourcing and believe the technology for rHA production can deliver this. Several customers have in fact already signed either letters of intent or supply agreements for the purchase of rHA. The rHA technology makes a better product.

- ***Ability to target molecular weight***. A final consideration is the ability for recombinant technology to deliver a more targeted and defined molecular weight for applications where HA plays a biological role in pharmaceutical applications. By using a well controlled production system, Novozymes has demonstrated the ability to target a specific molecular weight within a very narrow band. Until now this was not possible with the first and second generation production technologies at a large scale. Several companies have expressed a strong interest in this capability. Among the most exciting opportunities are applications for HA within the oncology field, where several studies have shown that very specific molecular weights of HA may have the potential to significantly increase the effect of oncology products and reduce the off-target effects through active targeting of tumor sites. It is believed this occurs in part through the binding of HA to the receptor CD44, thereby resulting in improved therapy options for cancer patients at a much reduced cost versus current targeted biologic therapeutics. The rHA technology makes better medicines.

Beyond the significant technological and health benefits to the U.S. from an improved source for HA, there are several other benefits that can be expected to directly result from a larger scale commercialization of this technology for cosmetic and medical applications:

- ***License fees***. The University of Oklahoma and Hyalose will both receive license income resulting from the sale of rHA products on a global basis. However, sales of HA in the U.S. market is the key driver for value in this case, and without sales in the U.S. market there would be no rationale for commercializing rHA in any other markets. Thus, the current focus is developing a commercial platform for production that can address the needs of the U.S. market.

- ***Increased availability and distribution of the technology***. A waiver will allow full-scale commercial production and increase the availability and distribution of the technology in cosmetic and health products to a greater population through major U.S. companies. Novozymes currently has a significant customer base willing and able to purchase and incorporate technical grade rHA for

cosmetic applications available to U.S. citizens including, (b)(4) Further, a waiver will allow for increased availability of higher quality HA for medical applications for the general public, including: visco-elastic devices for joint treatment, dermal fillers, adhesion prevention, ocular visco-elastic devices, dermatology, topical eye care, injectable drug delivery, cell therapy, cystitis, and haemostasis.

- ***Tax revenue.*** The commercialization of the rHA and sales in the U.S. will result in tax revenues for the Government.

- ***Job creation.*** The commercialization of rHA has the potential to create new jobs in the U.S. to facilitate the sale and distribution of the new product. For example, Novozymes alone has established a US commercial organization based in Boston (Novozymes Biopharma US), which currently has (b)(4) sales and sales support staff employed who are involved in the sale of rHA. As the business for HA expands, this group is expected to be further expanded to handle sales and sales support for rHA, resulting in further job creation opportunities over the next 5-10 years.

III. Possible U.S. Manufacturing Facilities Currently Do Not Exist

Unfortunately, as explained below, the benefits of the rHA technology will not be realized if the rHA is required to be manufactured in the U.S. Current HA manufacturing facilities are not set up for rHA production and do not have the necessary capacity and equipment.

A. Manufacturing Requirements

The manufacturing process for recombinant *Bacillus*-derived HA differs significantly from HA produced from the first and second generation processes where the recovery/purification processes are based on precipitation in organic solvents (*e.g.*, ethanol). The manufacturing process for recombinant *Bacillus*-derived HA draws on a mix of processes for biological pharmaceutical ingredients (API's), such as proteins and peptides, and biological polymers. Recombinant *Bacillus* HA manufacturing is based on standard fermentation conditions, which can be controlled in standard fermentation equipment for biological API's (proteins/peptides). Recovery/purification, however, is different from most biological API's. Although the equipment used is not uncommon, the recovery/purification process consumes a disproportionately large amount of filtration capacity and water compared to current biological API processes. The requirements for the bulk product formulation are also extraordinary compared to other biological API's as the *Bacillus* process involves spray drying, a process not commonly used for biological pharmaceutical ingredients. Moreover, the overall process (fermentation → recovery/purification → spray drying) has to be done as one continuous process because the liquid concentrate is not microbially stable during longer storage time. This means that all steps have to take place within the same plant. Finally, because of the medical applications for HA, it is necessary to manufacture HA in a facility with pharmaceutical quality controls (Q7 cGMP), which makes it very difficult to retrofit any non-pharmaceutical facility that would otherwise have been useful.

B. Lack of Capacity at Existing U.S. Facilities

Given the special needs for manufacturing of recombinant *Bacillus*-based HA, especially regarding spray drying, it has not been possible to identify existing production capabilities or capacity in the U.S.

After licensing the rHA technology from the University of Oklahoma, Hyalose LLC hired a consultant to perform market research to identify potential sublicensees for the technology. Hyalose LLC was able to identify eleven companies, many of which were foreign companies, with potential manufacturing capabilities. Hyalose LLC reached out to these companies, but was unable to identify any that had, or were willing to develop, full-scale production capabilities for the new technology. Further, existing U.S. facilities that were screened lacked the right equipment, setup and quality controls, and would thus require substantial retrofitting in order to be useful for rHA production. Indeed, there are no commercially relevant production facilities for cosmetic grade HA producers in the U.S. today.

IV. Assessment of Potential U.S. Manufacturing Options Reveals Domestic Manufacture of HA is not Commercially Feasible

Novozymes, which was not of the eleven companies originally identified by Hyalose LLC (likely due to the fact that Novozymes was not in the HA production business at the time), reached out to Hyalose LLC regarding a potential sublicense for the rHA. Some time thereafter, Hyalose LLC and Novozymes entered into a sublicense for the rHA technology and Novozymes initiated a major strategic review of manufacturing options for long term production of rHA. As set forth in greater detail below, in order to be able to deliver rHA to the U.S. and other markets, production of rHA will have to be placed outside of the U.S. in a lower cost region that allows for lower capital expenditure and lower running capital cost.

Because current U.S. facilities lack the capacity for rHA manufacturing, domestic manufacturing would require either (1) significant redesign and retrofitting of existing facilities at substantial cost, or (2) construction of an entirely new production facility dedicated for this product. Moreover, the operation costs alone of a U.S. facility, whether it be in a retrofitted or new facility, are commercially prohibitive and would ultimately increase the cost of rHA – potentially a very important medical ingredient.

A. Current Facilities Lack Ability to Manufacture rHA

Novozymes began producing rHA for technical applications at its enzyme production facilities in Denmark. Novozymes chose its Denmark facilities for production because they replicated the current production systems available in the U.S., and had food grade GMP equipment that could be adapted reasonably for large scale testing of the new HA production system. Novozymes' U.S. facility also was considered as a possible location for production, and while this facility has some of the equipment needed, it is designed only for production of technical enzyme products within feed, food and technical applications and cannot meet the general equipment and quality requirements for production of rHA.

In addition, Novozymes began testing for different HA applications, including cosmetics and eye care. The testing revealed that full scale production of rHA using the existing equipment at the current U.S. facilities (including Novozymes' Franklinton, North Carolina facility) would not be commercially feasible due to prohibitive costs and lack of suitable production capacity resulting from improper and inadequate equipment. Indeed, to date, production testing for HA at Novozymes' Danish facilities has shown a (b)(4) The conclusions of Novozymes' production testing are supported by the fact that there are no commercially relevant production facilities for cosmetic grade HA within the U.S.

B. Construction of New U.S. Manufacturing Facility Not Feasible

Building and operating a new U.S. facility is not commercially feasible based on cost estimates for U.S. pharmaceutical cGMP facilities and the costs associated with U.S. manufacturing operations when compared against the projected average sales price for HA. The cost of a new facility, even if at Novozymes' current site, where infrastructure, waste water treatment and basic utilities are in place, is estimated to be at leas (b)(4) The high investment cost, especially impacts return on investment in the first 3-4 years after launch, where volumes are low and the cost of goods sold ("COGS") exceed the average sales prices substantially. Although average sales price is predicted to climb above COGS long term, this return comes too late to cover the cost of the facility and furthermore is associated with a significant downside risk if average prices in the market drop further (a likely scenario as the patents covering rHA technology begin to run out in 2014 and forward). Regardless, even without the costs associated with construction of a new facility in the U.S., the operation costs alone make domestic manufacture of HA not commercially feasible.

Costs associated with production in U.S.

The total cost associated with production of HA can be divided into variable costs (*e.g.*, raw materials and utilities like electricity and steam consumption), fixed costs (*e.g.*, labor), depreciation of investments and other costs including sales, marketing and R&D support.

Variable costs

The raw material costs are assumed to be the same no matter where in the world the production is planned. This is because of the need for high quality/compendial grade raw materials. The variable costs are estimated on average to be approximately [redacted] kg HA.

Fixed costs

A major part of the fixed costs are labor costs. An organization and labor analysis was done for operations at a new facility on an existing site (area services such as security and area maintenance not included). The conclusion of the analysis indicates an organizational requirement of [redacted] full time employees in different positions to run a new HA facility with the requirements for quality, capacity and processes (see Table 1 below). Based on the average employee cost at Novozymes biotech enzyme production plant in Franklinton, North Carolina (see Table 2), labor costs alone for a domestic facility are estimated to be $8.09 million per year.

Table 1: Labor for new HA facility.

[redacted]

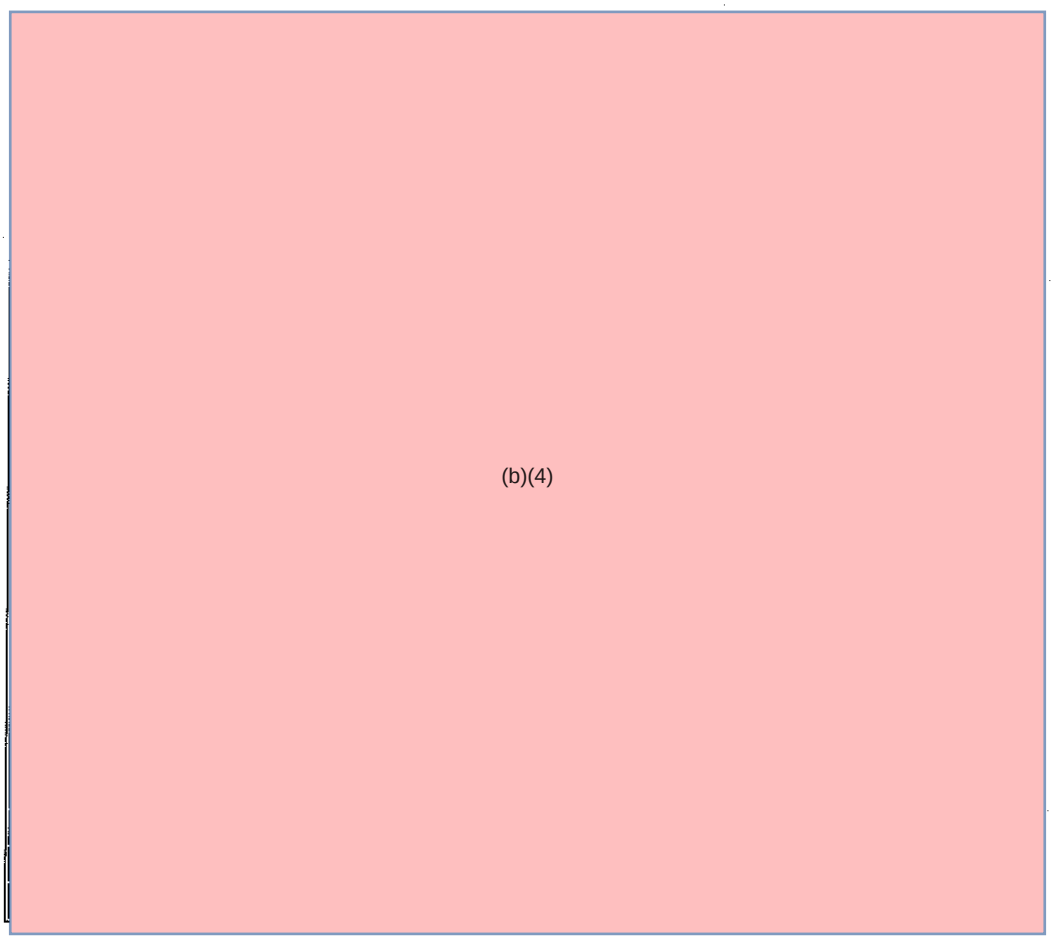
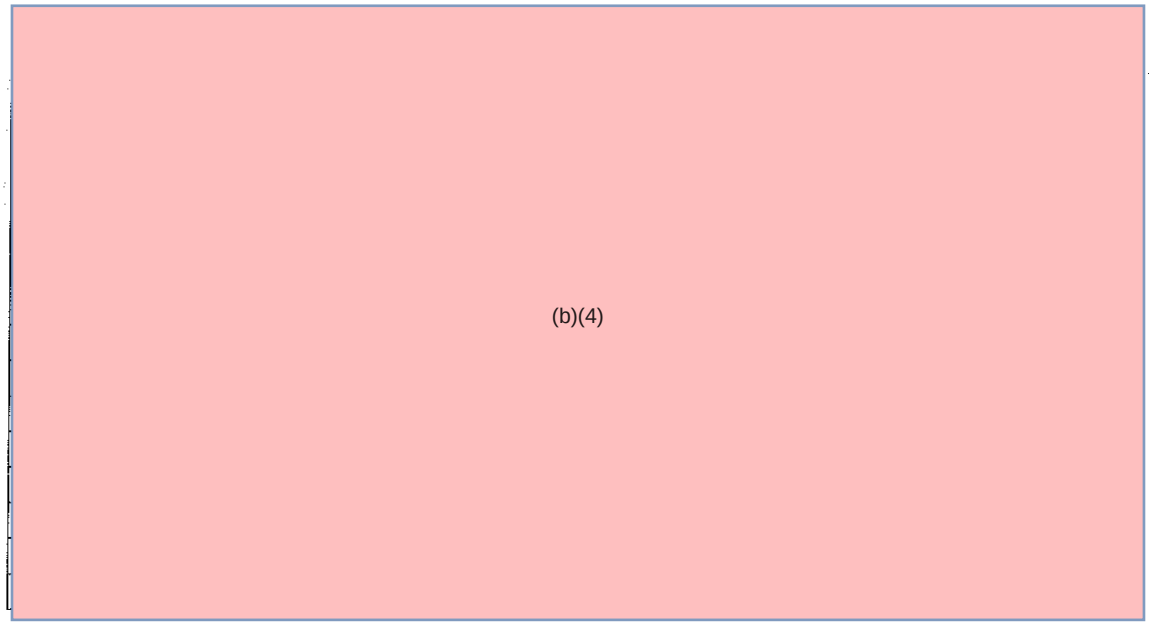


Table 2 Total average employer costs, Novozymes site in Franklinton, NC, 2009.
The average costs include salary/wages, Social Security, Medicare, Unemployment, Occupational Injury, Pension, Medical, Life & Accident Insurance and bonus.
Source: P&O, Novozymes, Franklinton, NC.



Cost of Goods sold (COGS) and sales prices

The resulting total costs of goods sold, including variable and fixed production costs, depreciation and other costs such as sales, marketing and R&D are in the range of (b)(4) kg HA, depending on volume (see figure 1 below).

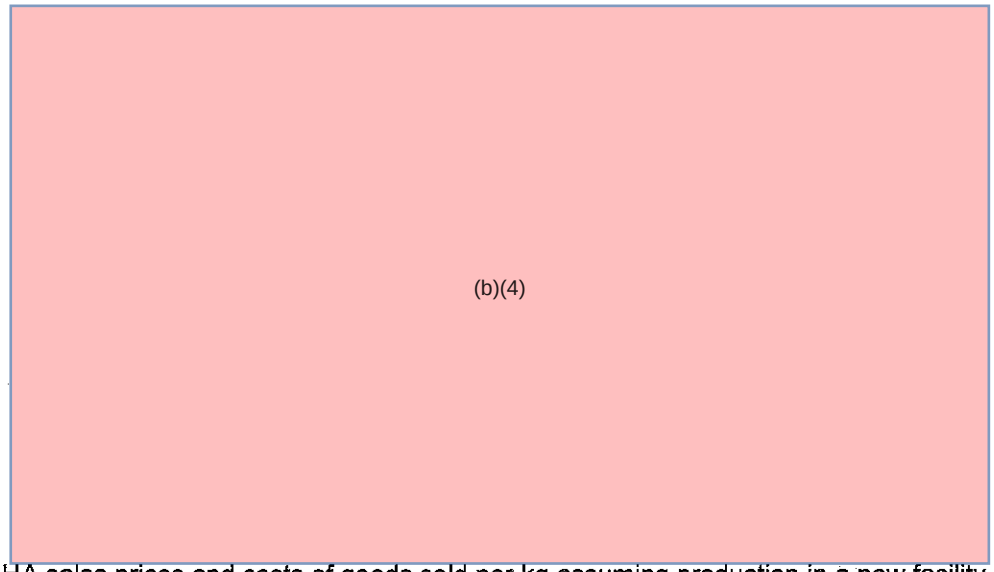


Figure 1. HA sales prices and costs of goods sold per kg assuming production in a new facility in U.S. on an existing site.

Given that average sales prices are expected to be in the range (b)(4) er kg HA (see figure 1 below) it has not been possible to develop a viable business case for establishing U.S.-based manufacturing. This conclusion also is reflected in the discounted cash flow models that Novozymes has used as a basis for a decision on manufacturing options. In this case, Novozymes' model yields a substantial negative return on investment and would lead Novozymes to stop all efforts in commercialization of the rHA technology.

The key issue here is the high investment cost, which especially impacts return on investment (b)(4) While the average sales price is predicted to climb above COGS long term, this return comes too late to cover the cost of the facility and is furthermore associated with a significant downside risk if average prices in the market drop further (a likely potential scenario as the patents covering rHA technology begin to run out in 2014 and forward).

V. Non-Domestic Manufacturing Would Allow Commercialization

In contrast, Novozymes has determined that manufacturing HA in a foreign location, such as China, would allow for financially viable commercial production due to lower capital and labor costs. For example, Novozymes has run a similar cost analysis exercise on facility construction in China, using the same raw material costs and the same expenditure for sales, marketing, R&D. The same requirements regarding quality, capacity, process and equipment were applied in the hypothetical, thus allowing a direct comparison between domestic and foreign facility investment costs and labor costs. As set forth below, non-domestic manufacturing makes commercial production possible.

Manufacturing in a new China facility on Novozymes' existing site

As with the cost estimates for domestic manufacturing, the foreign manufacturing cost estimates assume construction of a new facility at an existing Novozymes' site. Novozymes has non-occupied land in Tianjin, China with existing infrastructure, waste water treatment and basic utilities in place. Investment in a new facility on the existing site in Tianjin is estimated to be approximately the cost for a U.S. facility. Reference: NNE-Pharmaplan basic design cost estimates for China HA pharmaceutical cGMP facility.

Fixed costs

The organization set-up and labor numbers in China are assumed to be the same as in US estimate, however, there is a significant difference in average labor costs. Based on the average salaries for Novozymes' Tianjin site (see Table 3 below), the total labor costs for China have been calculated to (b)(4)

(b)(4)

Table 3: Total average employer costs, Novozymes site in TEDA, Tianjin, China 2008.
The average costs include salary/wages, government mandatory benefits (pension, medical insurance, unemployment insurance, occupational injury insurance, maternity leave and housing), bonus and Novozymes supplementary benefits.
Source: P&O, Novozymes, Tianjin, China.

Cost of Goods sold (COGS) and sales prices

The resulting total costs of goods sold, including variable and fixed production costs, depreciation and other costs including sales, marketing and R&D are in the range (b)(4) kg HA depending on volume (see figure 2). Based on expected sales prices, the overall business case for China is positive and with a reasonable margin for downside risks such as delays and price erosion. Moreover, obtaining reduced production costs will prevent significant product price increases for the consumer.

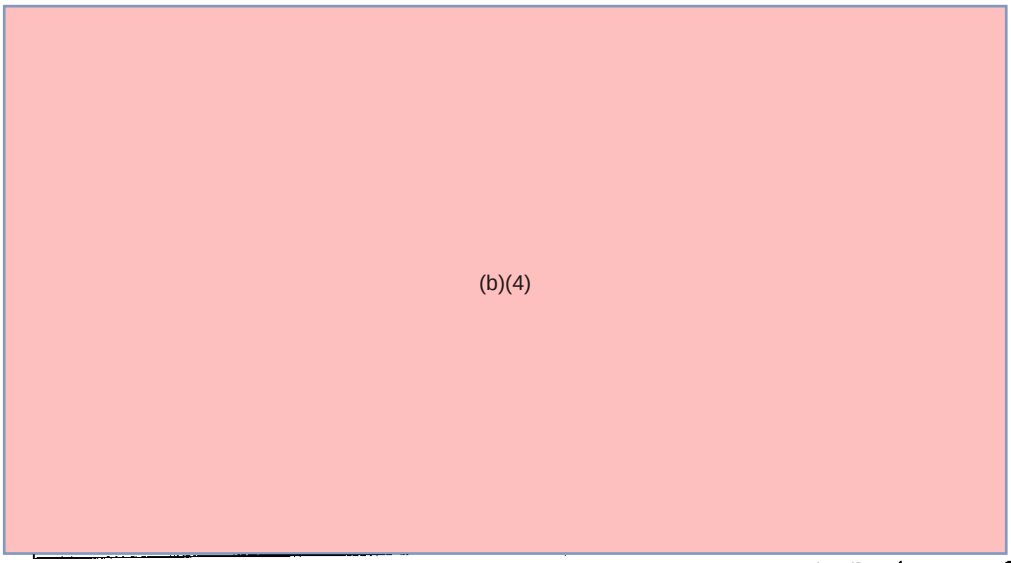


Figure 2. HA sales prices and costs of goods sold (COGS) per kg assuming production in a new facility in China on an existing Novozymes site.

VI. Summary

Substantially manufacturing rHA in the U.S. is not commercially feasible based on economics and logistics. The cost and economic analyses indicate that domestic rHA production cannot be profitable at the present time. Further, no existing U.S. facility currently is capable of manufacturing rHA. However, a domestic manufacturing waiver would allow Novozymes to proceed with full-scale production of rHA and bring an exciting and valuable product to U.S. consumers, including patients, at a lower cost. More importantly, the technology developed by The University of Oklahoma, in cooperation with Novozymes and Hyalose, has the potential to deliver a number of important benefits to both U.S. patients using HA-based products, as well as U.S. companies sourcing HA for medical and technical applications.

Therefore, the University of Oklahoma submits, and jointly with Novozymes and Hyalose hereby requests a waiver of the substantially manufactured clause.

Thank you for your attention to this matter. We look forward to hearing from you.

Colin M. FitzSimons
Associate Vice President for Technology Development
Executive Director, Intellectual Property Management Office

[i] Frost & Sullivan, U.S. and Western European Adhesion Prevention Products Market, April 2009. Millennium Research Group, Global markets for hyaluronic acid in aesthetic, orthopedic, ophthalmic, and emerging applications, 2008.
[ii] Kogan et al., Biotechnology Letters 2007, 29: 17-25
[iii] Nakano T, Sim JS, Poult Sci. 1994 Feb;73(2):302-7, Rooster comb and wattle tissues contain an anti-keratan sulfate monoclonal antibody epitope.
[iv] J Rheumatol., Sep 1990, 17(9):1230-6, Septic arthritis due to group C streptococcus: report and review of the literature.
[v] Chong BF, Blank LM, Mclaughlin R, Nielsen LK. Appl Microbiol Biotechnol. 2005 Jan; 66(4):341-51, Nov 13, 2004, Microbial hyaluronic acid production.
[vi] Friedman PM, Mafong EA, Kauvar AN, Geronemus RG. Dermatol Surg. 2002 Jun; 28(6):491-4, Safety data of injectable nonanimal stabilized hyaluronic acid gel for soft tissue augmentation.
[vii] ISTA Pharmaceuticals, Petition for Reconsideration Docket No. FDA-2008-P-0625, June 30, 2009.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

www.nih.gov

April 22, 2010

Mr. Colin M. FitzSimons
Associate Vice President for Technology Development
Executive Director, Intellectual Property Management Office
University of Oklahoma Health Science Center
Three Partners Place, Suite 100
201 David L. Boren Boulevard
Norman, OK 73019

Re: U.S. Patent Application No. 10/172,527

EIR #:1524003-01-0013 (Streptococcus Equisimilis Hyaluronan Synthase Gene and Expression Thereof in Bacillus Subtilis)
Patent Docket No.: 35541.048
P Title: HYALURONAN SYNTHASE GENES AND EXPRESSION THEREOF IN BACILLUS HOSTS
Inventor Names: Paul DeAngelis, Kshama Kumari and Paul Weigel,

Dear Mr. FitzSimons:

This letter is in response to the request for Waiver of the Preference for United States Industry (Manufacturing Waiver) submitted on behalf of the University of Oklahoma Health Sciences Center on the above-referenced invention derived or reduced to practice through an NIH funding agreement.

The waiver request has been approved as detailed in this letter. This Office concurs with the decisions of other offices involved in the approval process as listed below. This fact notwithstanding, should any of the particulars of the relevant exclusive licensing agreement change that could have potential impact on U.S. Manufacturing, you are required to inform this office of the changed circumstances.

Recommendation/Analysis

The technology described in this case is an improved method of generating hyaluronic acid, a critical protein used in a wide range of medical procedures and beauty products. The inventors discovered a means for engineering a harmless bacterium, *Bacillus subtilis*, to express the protein, rather than the pathogenic *Streptococcus equisimilis*, which is how the protein is currently made.

Unfortunately, while growing B. subtilis in fermentation tanks is a standard process, extracting the hyaluronic acid into a stable dry form is not. No facility in the United States suited for B. subtilis appears able to do the extraction, and retrofitting a plant while meeting cGMP requirements would be cost-prohibitive (building a new plant would be even worse). Novozymes can cost-effectively adapt a food-grade facility in Denmark to manufacture the products and meet cGMP requirements.

This waiver is for the use of the licensee's existing facilities only as discussed in the waiver request. At such time as those facilities become inadequate or insufficient, the Grantee must either require the licensee to develop manufacturing capacity inside the United States must request a further waiver of the Preference for United States Industry.

As compliance and oversight of this invention with the terms and conditions of the funding award continues, our office has noted your request in iEdison and you are also reminded that your institution must include this as part of its Utilization and Commercialization data from your licensees for the required Utilization Reporting via Interagency Edison at http://iEdison.gov. Any additional information related to this technology that may give rise to the possibility of U.S. Manufacturing should be promptly communicated to us. In addition, this waiver is valid for a three-year period from the date of this letter.

Also, please note that all other obligations of the Funding Agreement that gave rise to this Subject Invention remain in force. This includes, but is not limited to, compliance with the Sharing of Unique Research Resources, Public Access Policy, and Data Sharing Policy, under the terms of the funding agreement(s) you have received.

Please feel free to contact our office should you have any additional questions regarding this issue.

Sincerely,

John Salzman
Assistant Extramural Inventions Policy Officer
Division of Extramural Inventions and Technology Resources
Office of Policy For Extramural Research Administration, OER, OD

Please direct all correspondence to:
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Suite 310, MSC 7980
Bethesda, MD 20892-7980

Phone: (301) 435-1986
Fax: (301) 480-0272
e-mail: waiver@nih.gov

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original

University of Oklahoma Health Sciences Center

INVENTION DISCLOSURE

Please be as accurate and thorough as possible in supplying the information requested. For all requested dates, list month, day and year. When completed, the form should be delivered to the Office of Research Administration, LIB-121.

1. Title of Invention: **"Group C hyaluronan synthase gene and uses thereof"**

Full Name of Inventor: Paul H. Weigel, Ph.D.
Residence Address: 817 Hollowdale, Edmond, OK 73003 Citizen of: U. S.

Kshama Kumari, Ph.D. legal resident
Paul L. DeAngelis, Ph.D. US citizen

If more space is needed to list inventors, please add additional sheets giving the above information.

2. Invention disclosed or described in Lab Notebook(s):

(b)(4)

3. a. The invention was first conceived or thought of in a workable form on or about

(b)(4)

b. The invention was first disclosed to others on:

No disclosure to others before this present document.

c. The person(s) to whom the invention was first disclosed are:

(b)(4)

d. The first written description of the invention is in the form of _____date_____ and is now located _____:
Initial draft in progress of this document started on 3-26-97.

e. The first sketch or drawing of the invention was made on:
Not applicable

f. The first construction of the invention was begun on____**N/A**_____ and finished on_____.

In a project of this nature, it is difficult to give a meaningful answer to this question. August 24, 1996 was the first time a Group C DNA fragment was isolated, sequenced and concluded to be from the sought-after *has* gene. Numerous other leads and initially positive results did not enable isolation of the authentic gene.

g. The invention was first successfully tested on _____ and the test results are now located _____:

(b)(4)

h. The invention was first commercially used or sold on (date)_____**N/A**_____.

i. If a disclosure of the subject matter of the invention has been made in any publication, including a grant application, manuscript, abstract, catalog, report, advertising material or brochure, or if such disclosure is anticipated, identify and provide copies: **No disclosure has been made to date.**

(b)(4)

j. If there were any collaborators in this invention not listed as inventors, list their names and affiliation: **None.**

4. If there has been any non-confidential experimental use of the invention, explain giving dates and circumstances: **N/A**

5. To your knowledge: per SM disc w/PD and patents

a. Was any time charged to a Government Contract in *conceiving* this invention? ~~No.~~ NIH GM035978

b. Was any time or material charged to a Government Contract in reducing the invention to practice when it was first successfully built and operated? **No.**

c. At or about the time of conception or first actual reduction to practice, were you, any co-inventor, or anyone who assisted in such reduction to practice charging any time to a Government contract which called for experimental, develop-mental or research work on the problem solved by the invention? **No.**

d. At or about the time of conception or first actual reduction to practice, were you, or any co-inventors, supervising or advising anyone who was working under a Government contract which called for experimental, developmental or research work on the problem solved by the invention? **No.**

e. Is the invention embodied in any material or product finished or to be furnished under a Government contract? **No.**

6. Brief abstract of the invention: (read 7, before writing here):

7. Prepare and attach to this cover sheet a complete written disclosure of your invention including any sketches, diagrams, drawings, prints, etc. which will aid in understanding this invention. The outline below should be followed in writing the disclosure.

a. Brief discussion of problem solved by invention:

b. Presentation and discussion of known prior art, including manner in which others have attempted to solve the problem. Point out disadvantages and weaknesses in prior art. Include literature references and copies where available.

c. Description of invention, including a specific embodiment. Point out important features and points believed to be novel. State advantages of invention and sacrifices, if any, made to achieve these advantages. Described any experiments conducted and the results of those experiments.

d. Is the concept of the invention applicable to other problems and fields of interest? If so, what are they and how would the principles of the invention be used?

e. What commercial products(s) might result from this invention? Who would purchase the product(s)? What is the potential annual market value of the product(s) (please justify your market estimate as best you can)?

8. The invention described by the attached patent disclosure is submitted pursuant to my Employment Agreement with the University of Oklahoma Health Sciences Center:

Inventor(s) Paul Weigel Date 3-31-97
Paul H. Weigel, Ph.D.

Kshama Kumari Date 3 · 31 · 97 ·
Kshama Kumari, Ph.D.

Paul L. DeAngelis Date 3/31/97
Paul L. DeAngelis, Ph.D

Contact person for more data: Paul H. Weigel, Ph.D. Telephone # hone #, Persona (Home)
271-1288 (Work)

Mailing Address: Personal Info

For Office of Research Administration use only:

5820.521

Date Received: 4/01/97 Docket #: 97HSC020

FNN: Yes ____ No ✓

OUHSC 01/95

ABSTRACT

"Group C hyaluronan synthase gene and uses thereof"

a) The invention enables at least four possible uses of the *Streptococcus equisimilis* nucleic acid segment encoding the gene product hyaluronan (HA) synthase, an enzyme that synthesizes HA.

(i) The gene can be used to construct bacterial strains that will produce and secrete HA for commercial production of HA. Overproducing strains or strains that make HA in a desired size range could have commercial advantages over existing strains.

(ii) The expressed recombinant protein, the seHAS, can be modified by genetic engineering to enable production of short HA (applicable for possible use as an angiogenesis agent) either by bacteria or by the recombinant enzyme in vitro.

(iii) Specifically engineered seHAS can be used to create novel carbohydrate polymers related to HA by incorporation of sugars other than the two natural precursors.

(iv) nucleic acid segments can be used to make PCR primers or probes to identify the presence of such sequences in various samples.

b) HA is produced worldwide by over a dozen companies either by extraction from rooster combs or by bacterial fermentation. HA is used in eye surgery, wound healing products, cosmetics, and dental adhesives. Products in development include intra-articular injections for arthritis patients and derivatives of HA as wound healing dressings, bio-compatible materials or as drug delivery vehicles.

The enclosed related patent application describes the prior art. That patent apparently will not cover several possible applications using the present seHAS. In addition, use of the recombinant enzyme in vitro and the use of specifically altered forms of the enzyme are not covered by the claims that were finally allowed in February 1997.

c) The attached data indicate the nucleic acid sequence and predicted protein sequence of the seHAS, as well as evidence for the synthesis of HA by isolated membranes.

d) Other possibilities remain open.

e) Medical uses for HA continue to grow. Annual HA sales are probably on the order of $100 million range world-wide, but this HA is then used in a variety of formulations and sold as other products. One potential market, not explored by current producers is the synthesis and use of smaller HA fragments, which appear to be angiogenic. Most present applications, such as for ophthalmologic use, require very high molecular HA. We would like to seek coverage on both size formulations of HA using specifically modified enzyme.

```
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seHAS ORF Nucleic acid sequence

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Range : 1 - 1254 Mode : Normal
Codon Table : Universal

```
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               63          72          81          90          99         108
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    --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
    Leu Leu Ile Tyr Val Asn Val Tyr Leu Phe Gly Ala Lys Gly Ser Leu Ser Ile

              117         126         135         144         153         162
    TAT GGC TTT TTG CTG ATA GCT TAC CTA TTA GTC AAA ATG TCC TTA TCC TTT TTT
    --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
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    --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
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              225         234         243         252         261         270
    TCT TAT AAC GAA GAT GCT GAG TCA TTG CTA GAG ACC TTA AAA AGT GTT CAG CAG
    --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
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              279         288         297         306         315         324
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    --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
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              333         342         351         360         369         378
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    Thr Gly Ile Lys Arg Ile Glu Asp Tyr Val Arg Asp Thr Gly Asp Leu Ser Ser

              387         396         405         414         423         432
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    --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
    Asn Val Ile Val His Arg Ser Glu Lys Asn Gln Gly Lys Arg His Ala Gln Ala

              441         450         459         468         477         486
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    --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
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              495         504         513         522         531         540
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--- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
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          603                 612                 621                 630                 639                 648
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--- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
Thr Arg Leu Thr Asp Ile Arg Tyr Asp Asn Ala Phe Gly Val Glu Arg Ala Ala

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--- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
Gln Ser Val Thr Gly Asn Ile Leu Val Cys Ser Gly Pro Leu Ser Val Tyr Arg

          711                 720                 729                 738                 747                 756
CGC GAG GTG GTT GTT CCT AAC ATA GAT AGA TAC ATC AAC CAG ACC TTC CTG GGT
--- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
Arg Glu Val Val Val Pro Asn Ile Asp Arg Tyr Ile Asn Gln Thr Phe Leu Gly

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ATT CCT GTA AGT ATT GGT GAT GAC AGG TGC TTG ACC AAC TAT GCA ACT GAT TTA
--- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
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          819                 828                 837                 846                 855                 864
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--- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
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          873                 882                 891                 900                 909                 918
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--- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
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--- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
Ser Ile Ile Ser Val Lys Lys Ile Met Asn Asn Pro Phe Val Ala Leu Trp Thr

          981                 990                 999                1008                1017                1026
ATA CTT GAG GTG TCT ATG TTT ATG ATG CTT GTT TAT TCT GTG GTG GAT TTC TTT
--- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
Ile Leu Glu Val Ser Met Phe Met Met Leu Val Tyr Ser Val Val Asp Phe Phe

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--- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
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AAA TTA TTA TAA 3'
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Lys Leu Leu ***
```

File: SEHAS.AMI
Range: 1 - 418
Molecular Weight: 47774.88

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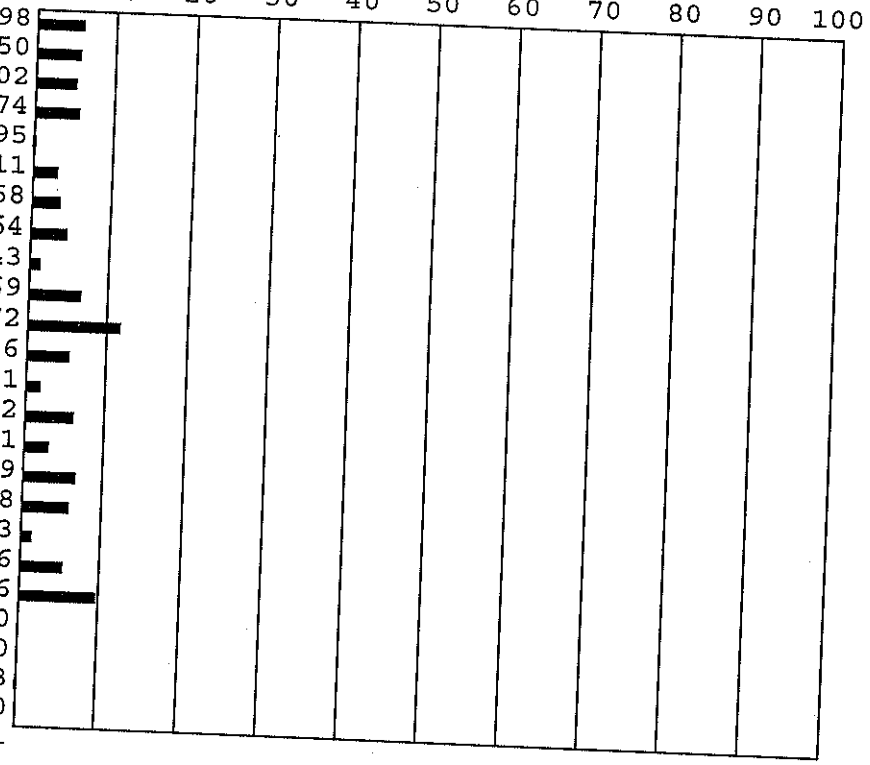
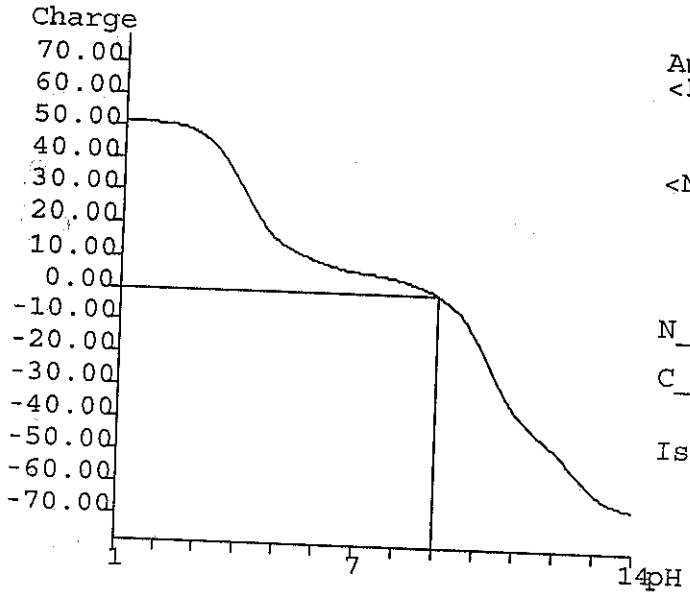
Arg	R	23	5.50
Asn	N	21	5.02
Asp	D	24	5.74
Cys	C	4	0.95
Gln	Q	13	3.11
Glu	E	15	3.58
Gly	G	19	4.54
His	H	6	1.43
Ile	I	28	6.69
Leu	L	49	11.72
Lys	K	22	5.26
Met	M	8	1.91
Phe	F	26	6.22
Pro	P	13	3.11
Ser	S	28	6.69
Thr	T	25	5.98
Trp	W	6	1.43
Tyr	Y	22	5.26
Val	V	40	9.56
Asx	B	0	0.00
Glx	Z	0	0.00
***	*	1	0.23
Xxx	X	0	0.00
Total		418	99.91



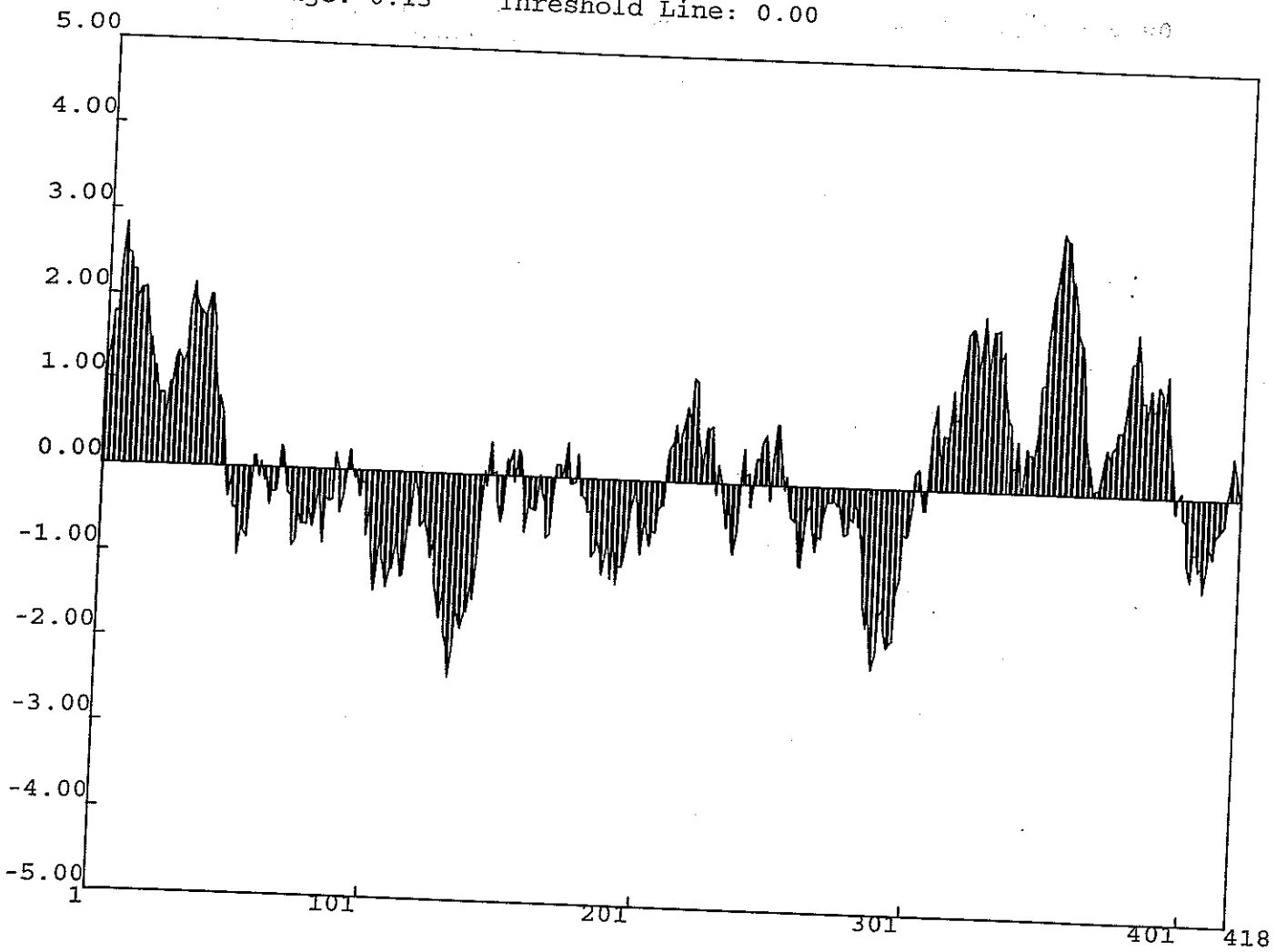
File : SEHAS.AMI
Range : 1 - 418



Amino Aci	Number	pKa
<Positive>		
Arg(R)	23	12.5
His(H)	6	6.0
Lys(K)	22	10.5
<Negative>		
Asp(D)	24	3.9
Cys(C)	4	8.3
Glu(E)	15	4.3
Tyr(Y)	22	10.1
N_terminal	Met(M)	9.3
C_terminal	***(*)	0.0

Isoelectric point [pI] 9.01

File: SEHAS.AMI 1 - 418
Table: Kyte & Doolittle
Window: 15 Average: 0.13 Threshold Line: 0.00



File1: SPHAS.SEQ
Mode: Normal
File2: SEHAS.SEQ
Mode: Normal
Matching Percentage (Total Window: 70%, Alignment Window: 70%)

```
-1   ..GTGC-CTATTTTTAAAAAAACTT-TAATTGTTTTATCCTTTA-T-TTT      1 -    1260
      | |  | |||   ||||||  ||  ||| ||||  |  |||||| | |||    1 -    1254
 1   ATGAGAAC-ATT---AAAAAACCTCATAACTGTTGTGGCCTTTAGTATTT

 49  TTTGA-TATCTATCTTGATTTATC-TAAATATGTATCTATTTGG----AA
     ||||  ||  ||  |  | ||||||  |  | |||  | |||||  |||||    ||
 51  TTTGGGTA-CTGT-T-GATTTA-CGTCAATGTTTATCTCTTTGGTGCTAA

 99  CATCAA-CTGTAGG-AATTTATGGAGTAATAT--TAATAACCTATCTAGT
      |  ||  ||  |  |  |||||||||  |  |  |  | |||  | ||  ||| |
101  -AGGAAGCT-T-GTCAATTTATGGCTTT-T-TGCTGATAGCTTACCTA-T

149  TA-TCAAACTTGGA-TTATC-TTTCCTTTATGAGCCATTTAAAGGAAATC
     ||  |||||  |  |   |||||  |||  ||||  ||||||||||  ||||
151  TAGTCAAAAT-GTCCTTATCCTTTT-TTTACAAGCCATTTAAGGGAAGGG

199  CACATGA-CTATA-AAG-TTGCTGC--TGTAATTCCTTCTTATAATGAAG
      |   ||  | |||  |||  ||||  ||  |  ||  ||||  ||||||||  ||||
201  C---TGGGCAATATAAGGTTGCAGCCAT-TA-TTCCCTCTTATAACGAAG

249  ATGCCGAGTCATTATTAGAAACACTTAAAAGTGTGTT-AGCA-CAGACCT
     ||||  ||||||||  ||||  ||  |||||||  |||||  ||||  ||  ||||
251  ATGCTGAGTCATTGCTAGAGAC-CTTAAAAA-GTGTTCAGCAGCAAACCT

299  ATCCGTTATCAGAAATTTATATTGTTGATGATGGGAGTTCA-A--ACACA
     ||||  ||  ||||||||||  |||||||  |||||  |||  |  |  |  |||
301  ATCCCCTAGCAGAAATTTATGTTGTTGACGATGGAAGTGCTGATGAGACA

349  GATGCAATACAATTAA-----TTGAAGAGTATGTAAATAGAGAAGTGGAT
      |  |  ||  ||||  |||||||  |||||  |  ||  |  |||  |
351  G--G---TA---TTAAGCGCATTGAAGACTATGTGCGT-GACAC-TGG-T

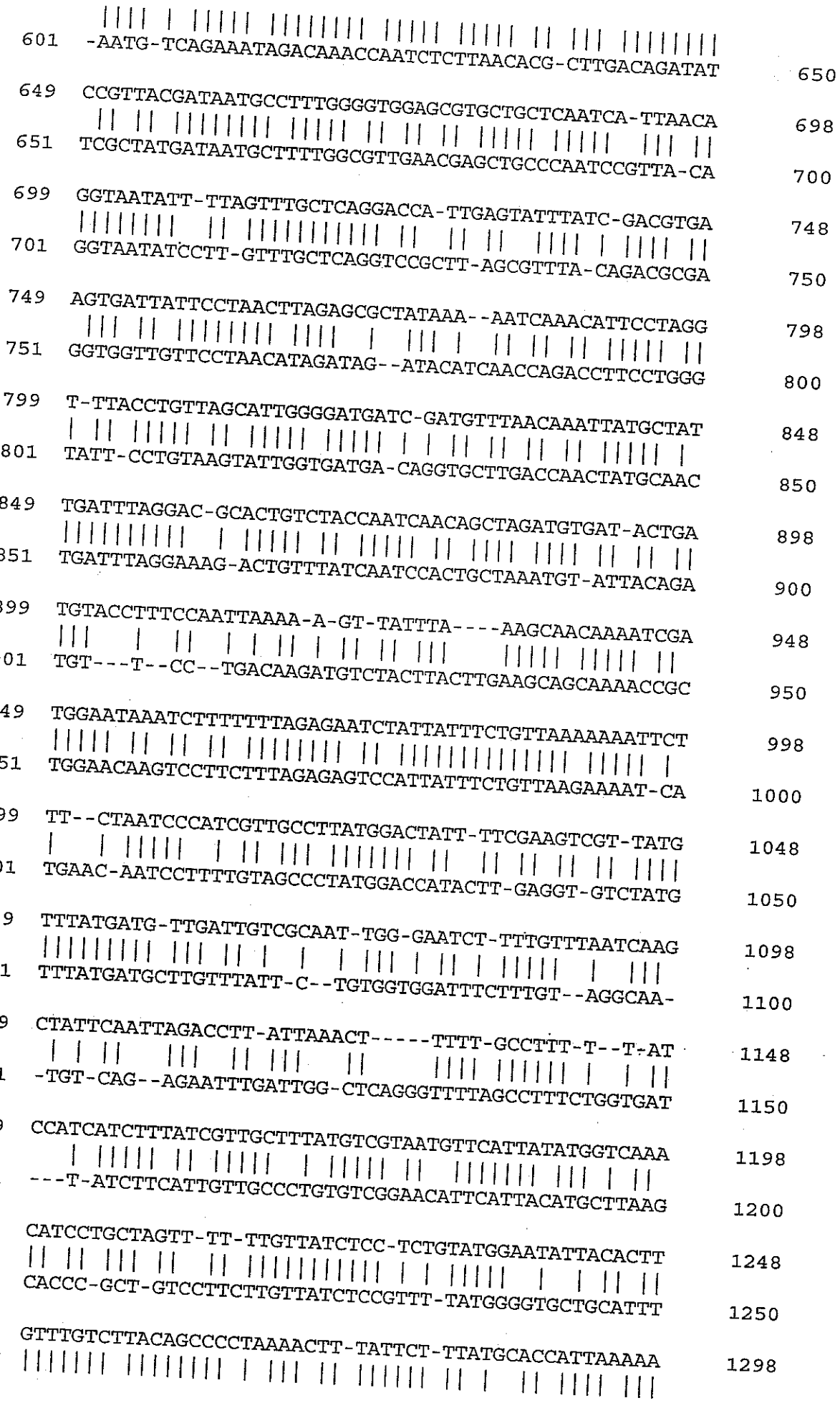
399  -ATTTGTCGA--AACGTTATCGTTCACCGTTCCCTTGTCAA-TAAAGGAA
      |  |  ||  |  ||  ||  ||  |||||  ||  ||  |  ||  |  ||||||
401  GACCTATCAAGCAATGTCATTGTTCATCGGTCAGA-GAAAAATCAAGGAA

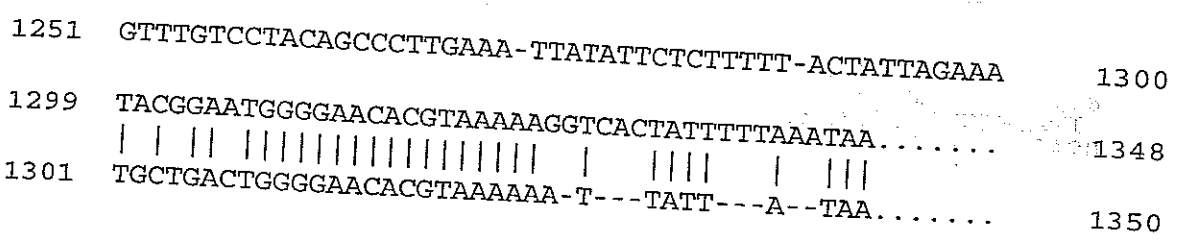
449  AACGCCATGCTCAAGCGTGGGCATTTGAAAGATCTGACGCTGACGTTTTT
     |  ||  |||||  ||  ||  |||||  ||||||||||  ||||||||  ||  |||
451  AGCGTCATGCACAGGCCTGGGCCTTTGAAAGATCAGACGCTGATGTCTTT

499  TTAACCGTAGACTCAGATACTTATATCTATCCAAATGCCTTAGAAGAACT
     ||  |||||  ||||||||||||||||||||  ||  ||||  |||||  ||  |
501  TTGACCGTTGACTCAGATACTTATATCTACCCTGATGCTTTAGAGGAGTT

549  CCTAAAAAGCTTCAATGATG-AGACAGTTTATGCTGCAACAGGACAT-TT
       ||||||  |||  |||||   |  ||  ||||  ||||||  ||  ||  ||  ||
551  GTTAAAAACCTTTAATGACCCA-ACTGTTTTTGCTGCGACGGGTCACCTT

599  GAATGCT-AGAAACAGACAAACTAATCTATTAACGCGACTT-ACAGATAT
```




1251 GTTTGTCCTACAGCCCTTGAAA-TTATATTCTCTTTTT-ACTATTAGAAA 1300
1299 TACGGAATGGGGAACACGTAAAAAGGTCACTATTTTTAAATAA..... 1348
1301 TGCTGACTGGGGAACACGTAAAAAA-T---TATT---A--TAA..... 1350

File1: SEHAS.AMI
1 - 418
File2: SPHAS.AMI
1 - 420
Matching Percentage (Total Window: 72%, Alignment Window: 72%)

```
   0  .MRTLKNLITVVAFSIFWVL---LIYVNVYLFGAKGSLS-IYGFLLIAYL      49
   1  VPIFKKTLI-VLSF-IF--LISILIYLNMYLFGT--STVGIYGVILITYL

  50  LV-KMSLSFFYKPFKGRAGQYKVAAIIPSYNEDAESLLETLKSVQQQTYP      99
  51  -VIKLGLSFLYEPFKGNPHDYKVAAVIPSYNEDAESLLETLKSVLAQTYP

 100  LAEIYVVDDGSADETG-IKRIEDYV-RDTGDLSSNVIVHRSEKNQGKRHA     149
 101  LSEIYIVDDGSSN-TDAIQLIEEYVNREV-DICRNVIVHRSLVNKGKRHA

 150  QAWAFERSDADVFLTVDSDTYIYPDALEELLKTFNDPTVFAATGHLNVRN     199
 151  QAWAFERSDADVFLTVDSDTYIYPNALEELLKSFNDETVYAATGHLNARN

 200  RQTNLLTRLTDIRYDNAFGVERAAQSVTGNILVCSGPLSVYRREVVVPNI     249
 201  RQTNLLTRLTDIRYDNAFGVERAAQSLTGNILVCSGPLSIYRREVIIPNL

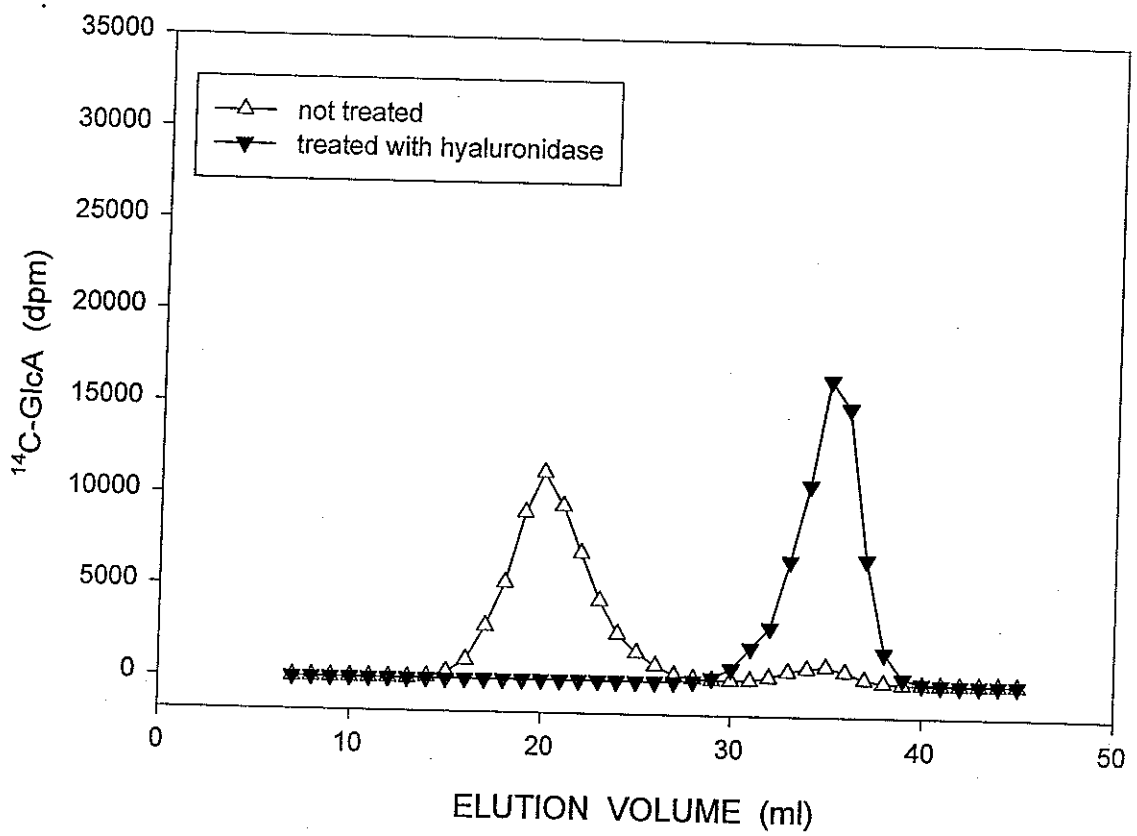
 250  DRYINQTFLGIPVSIGDDRCLTNYATDLGKTVYQSTAKCITDVPD--KMS     299
 251  ERYKNQTFLGLPVSIGDDRCLTNYAIDLGRTVYQSTARCDTDVPFQLK-S

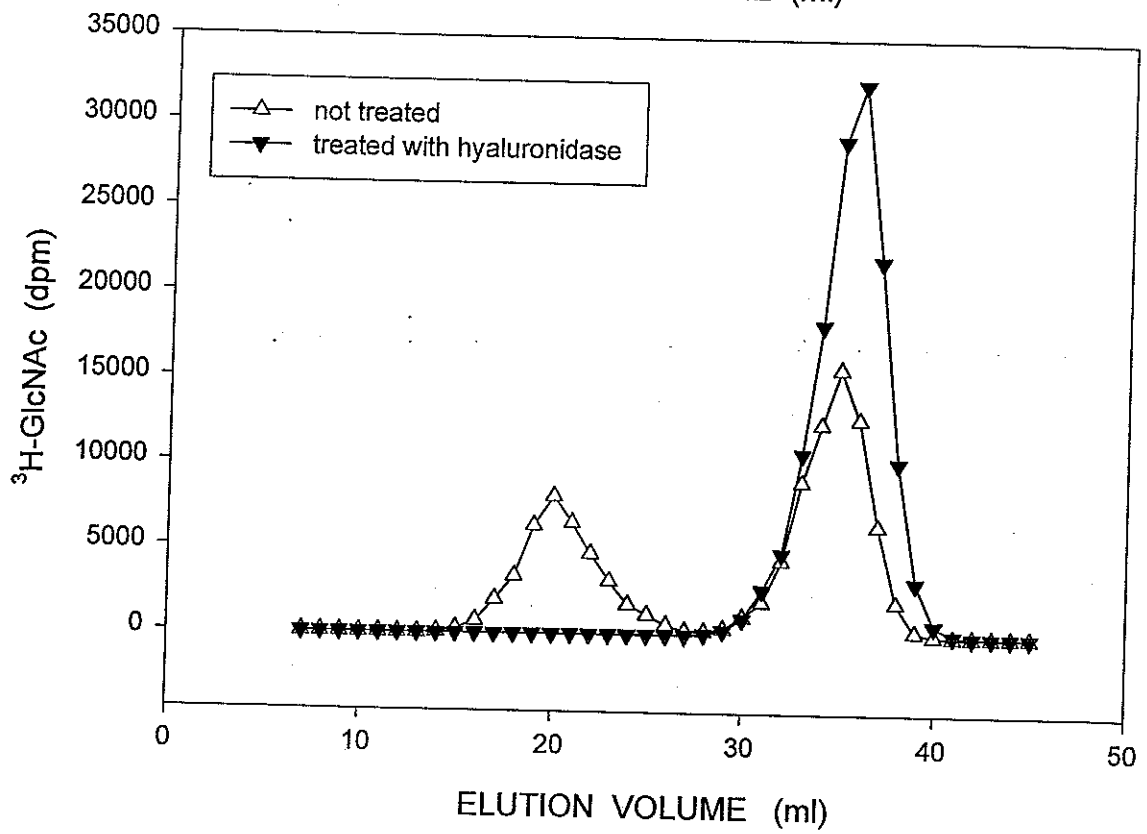
 300  TYLKQQNRWNKSFFRESIISVKKIMNNPFVALWTILEVSMFMMLVYSVVD     349
 301  -YLKQQNRWNKSFFRESIISVKKILSNPIVALWTIFEVVMFMMLI--VAI

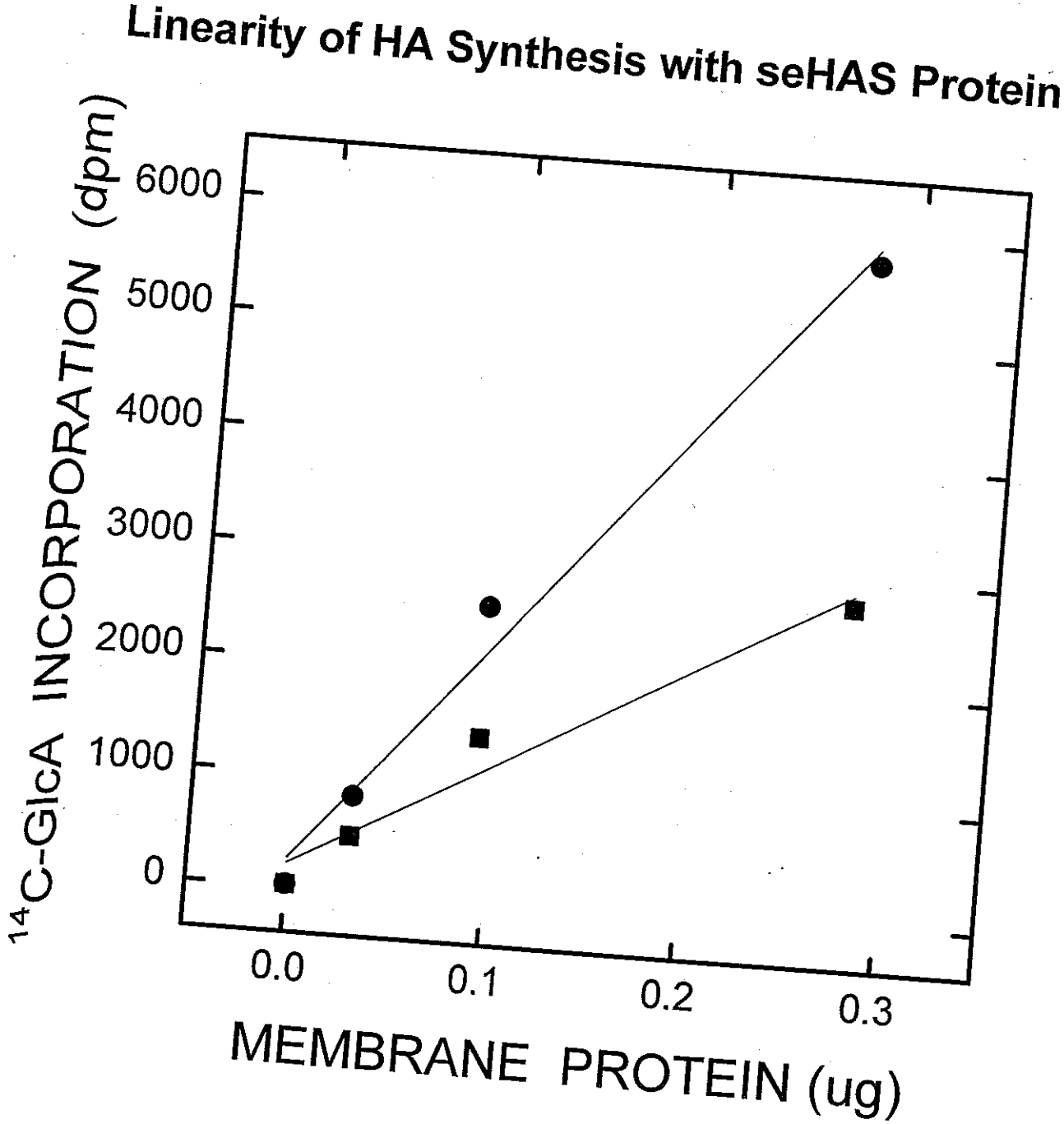
 350  FFVGNVREF------DWLRVL-AFLVIIFIVALCRNIHYMLKHPLSFLLS     399
 351  ---GNLL-FNQAIQLD-LIKLFAFLSIIFIVALCRNVHYMVKHPASFLLS

 400  PFYGVLHLFVLQPLKLYSLFTIRNADWGTRKKLL---*.............     449
 401  PLYGILHLFVLQPLKLYSLCTIKNTEWGTRKKVTIFK*.............     450
```

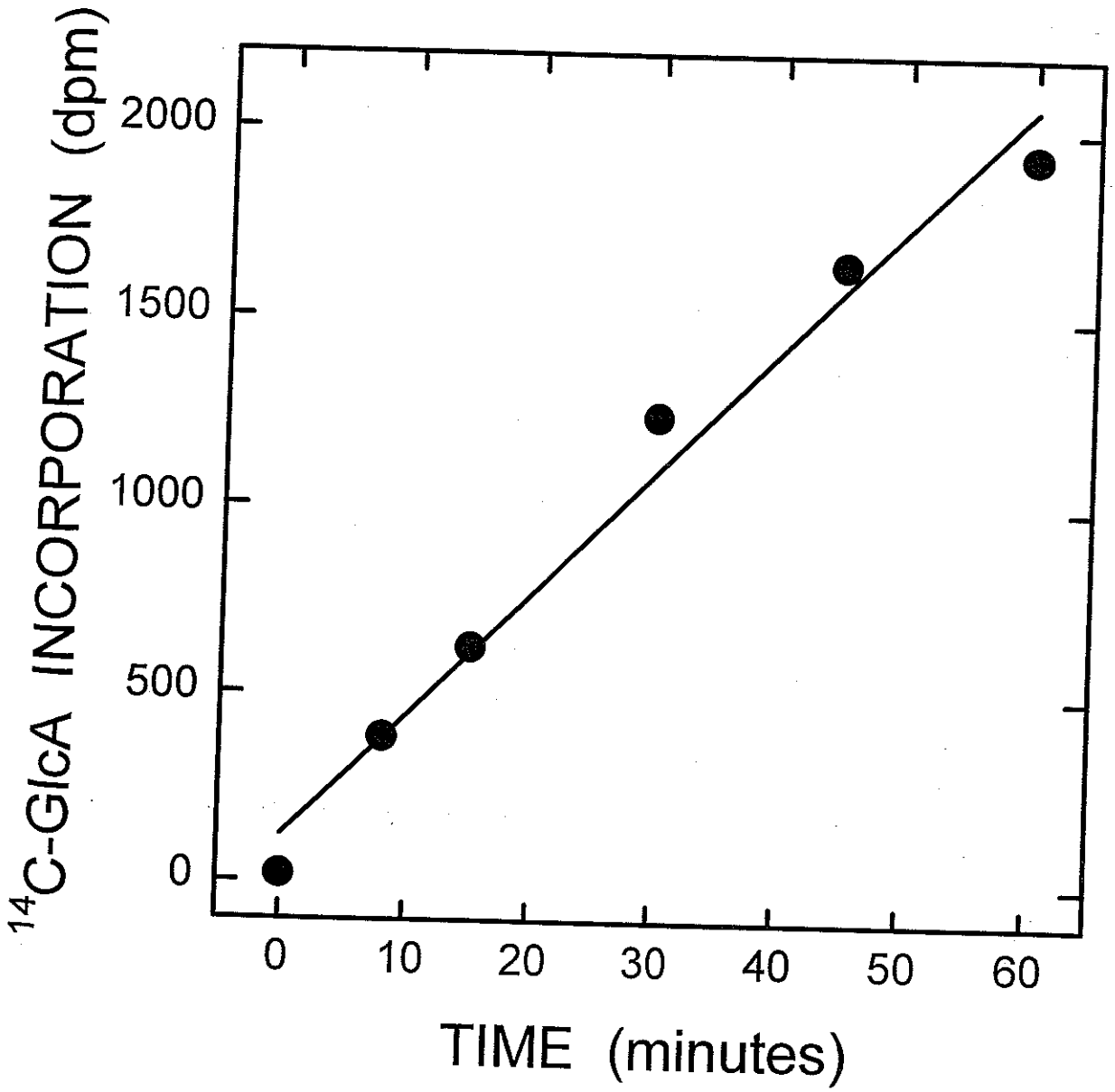
Gel Filtration of Hyaluronan synthesized by seHAS






Linearity of HA Synthesis with seHAS Protein
^{14}C-GlcA INCORPORATION (dpm)
6000
5000
4000
3000
2000
1000
0
0.0
0.1
0.2
0.3
MEMBRANE PROTEIN (ug)

Linearity of HA Synthesis by seHAS with Time



Pages 179 through 1939 redacted for the following reasons:

Removed by agreement