

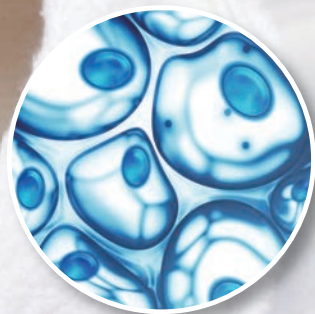
N A T U R A L P R O T E O G L Y C A N

The miracle compound

# Natural Proteoglycan



Interviewee  
Biomatec Japan  
Yoshiaki Kudo



The Monozukuri Nippon Grand Award “Prime Minister's Award”  
Extracted with the world's only technique LPT  
Being realized its purity **90%** to maximize the  
proteoglycan's original functionality.

# The miracle compound Natural Proteoglycan

With the world's only technique LPT,  
proteoglycan has been dramatically improved

As an ingredient that approaches cells themselves to work on fundamental causes of every kind of disorders, proteoglycan is noted in various fields as healthcare foods, cosmetics and other medical care industries.

It has become noticed after the extraction technique has been developed in Japan in 2003, which has enabled its mass production.

After that continuous efforts by researchers have been made to improve the technique more and more, which has finally enabled mass production of proteoglycan in higher purity without losing any of its functionality.

This is the brief story how proteoglycan has been produced.

This booklet will show you its huge possibility based on an interview to Yoshiaki Kudo, the parent of proteoglycan who has established LPT (Leave Protein Technology) , the world's only technique by developing an innovative technique.

## Yoshiaki Kudo

President and CEO of Biomatec Japan, Inc.

Born on 28 April, 1942 in Aomori pref, Japan.

Graduated from Sapporo West High School and Waseda University (political science and economic department)

Worked for Kakuhiro Corporation from 1972.

Started his study of proteoglycan at the planning and development section of the same company from 1998.

Continued his study in their research laboratory in Kushiro from 2002, but resigned this company in 2005 at the timing of their withdrawing of operations.

Kept working on his study on his own and found a new extraction technique of proteoglycan in November, 2005 and acquired its patent.

Founded Biomatec Japan in May, 2006.

\*This book is composed based on an interview to Mr. Yoshiaki Kudo as well as his lectures or research documents.

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# History of Mr. Yoshiaki Kudo and the development of natural proteoglycan

July, 1998	As an employee of Kakuhiro Corporation, started studying on mass production of proteoglycan in collaboration with Hirosaki University
March, 2003	Established a mass production technique by extracting proteoglycan out of salmon nasal cartilages
February, 2005	Resigned Kakuhiro Corporation at the timing of their withdrawing of operations and started his own study on original extraction technique
May, 2006	Founded Biomatec Japan, Inc. Contracted on a joint study with the Kushiro Industrial Technology Center
November, 2006	Contracted on a joint study with Hokkaido University
February, 2007	Applied to an international patent
June, 2007	Passed the cosmetics safety test
August, 2007	Adopted the Regional resource utilization type Research and Development Project, the METI commissioned project
October, 2008	Being approved the Japanese patent No.4219974
December, 2008	Received a thank-you letter from the governor of Hokkaido for the cooperation to the Hokkaido Toyako Summit
June, 2009	Adopted the Practical technology development projects to promote the new Agriculture, Forestry and Fisheries Policy, the MAFF commissioned project
November, 2009	Won the Hokkaido New Technology and New Product Development Award, the Monodzukuri Section Encouragement Award
October, 2010	Being approved the Russian patent No.2401839
September, 2011	Acquired the HALAL certification
February, 2012	Won the Monozukuri Nippon Grand Award "Prime Minister' s Award"
April, 2012	Being approved the US patent No.8153769
May, 2012	Gave a lecture on the possibility of proteoglycan at the Sapporo Stock Exchange
October, 2012	Won the Encouragement Award of Small and Medium Enterprise at the prize-giving ceremony 2012 by the Institute of Invention
October, 2012	Proteoglycan exhibited in the 2012 annual meeting of IMF, the government-sponsored exhibition, nominated by the Ministry of Finance
November, 2012	Televised by NHK in a nation-wide network program

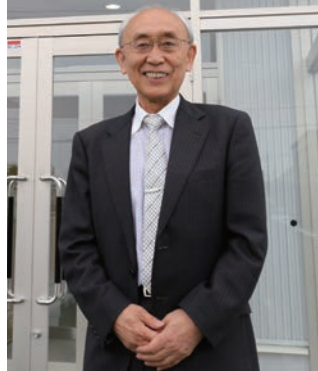
# Mr. Kudo speaks on what is natural proteoglycan

The development process  
and its superiority



## The world-first mass production of acetic acid The process to practically apply proteoglycan

Study on structure or bioactivities of proteoglycan had been continued since 1970s, which had been greatly expected its application to medical and pharmaceutical products, health foods and cosmetics. However, no effective extraction technique having been established as well as its selling price being very expensive to be **more than 30 million yen per gram**, it was quite unreasonable to use for consumer products.



At the end of 20c, the research team led by Professor Keiichi Takagaki from Hirosaki University had finally resolved this difficult problem.

In 1998, a joint project to develop a mass production technique of proteoglycan was proposed by Hirosaki University to Kakuhiro Corporation which I had been working for at that time, and I was chosen to the person in charge of that project.

Though I was a complete beginner in medical field, I started studying in Hirosaki University medical department at the age of 55 to learn proteoglycan from nothing.

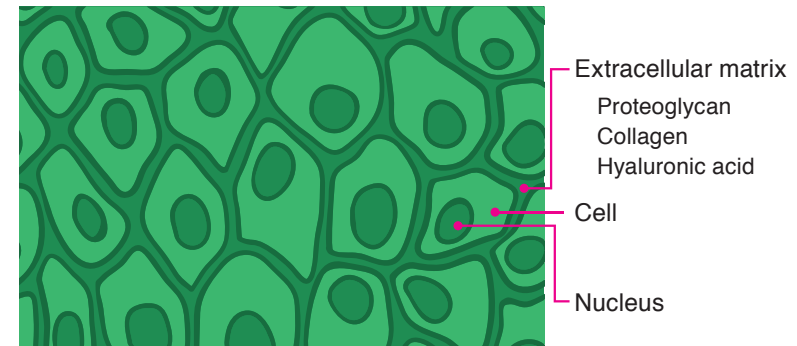
I have learned that **biological activities by all the animals including human beings are supported by proteoglycan from the back, which plays a significant role for their health.**

So artificially mass producing it will be so much valuable, with which interested me much as I was sure that it will greatly contribute to medical field.

And finally in 2003, **I was successful in finding a mass production technique of proteoglycan by acetic acid extraction**, being researched with Professor Takagaki from Hirosaki University and others.

Thanks to that I could have realized a breakthrough pricing as 300 thousand yen per gram.

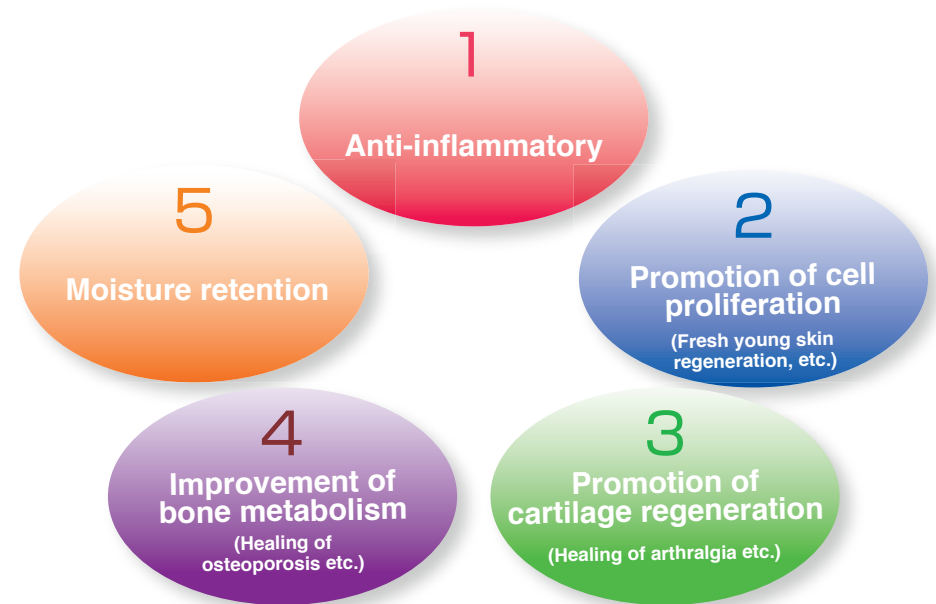
### Proteoglycan to govern extracellular matrix



Between the cells there is a jelly like substance which is called extracellular matrix. Common ingredients that compose this extracellular matrix are hyaluronic acid and collagen, but it has revealed that proteoglycan is the most important ingredient between them.

**Not only high moisture retention, it brings about promotion of skin regeneration (same effect as EGF) by generating additional collagen and hyaluronic acid.**

### The revealed physiological function of proteoglycan





## Proteoglycan is disconnected on the way? Difficulties in cost and technical challenges

Cost reduction from 30 million yen per gram to 300 thousand yen per gram is a really wonderful result. I have visited health food and cosmetic companies across Japan by flying more than 100 times a year with samples of proteoglycan.

Everybody in charge of technology or product development was greatly interested in it, but no managements said yes, as for manufacturers the reasonable price is 1,000 yen per gram to use it for their merchandises. They said that **even 300 thousand yen per gram is too expensive.**

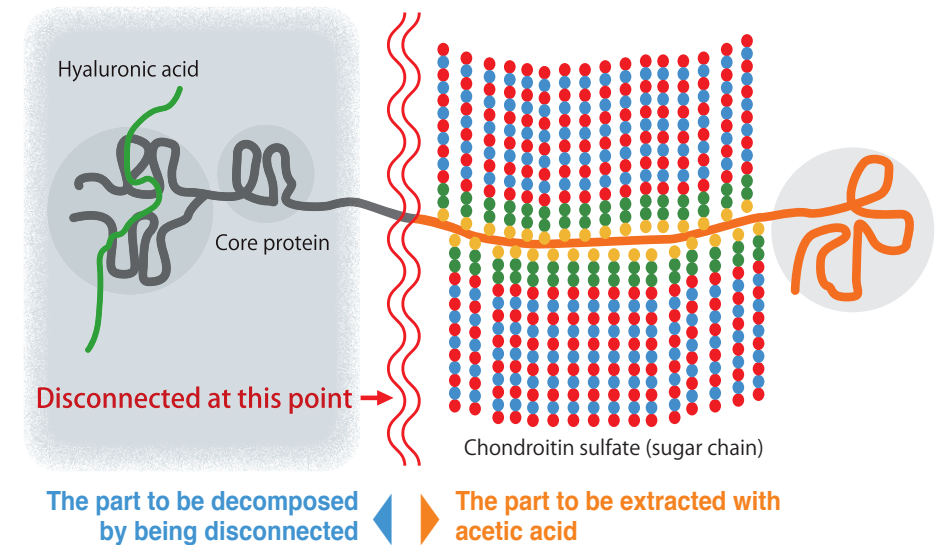
February 2005, Kakuhiro Corporation has decided their withdrawal from proteoglycan business as they could have got no order even after investing much money on its development. But I could not give up realizing **mass production of proteoglycan as my dream.**

I'm approaching the goal. **Proteoglycan is sure to be essential for human body** so its mass production is useful for people and society. This was my belief that made me resign this company and decide to keep studying on the research on my own.

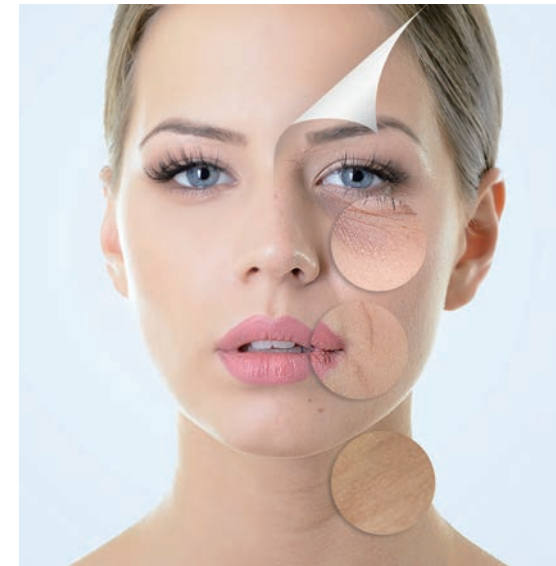
This was a starting up at the age of 64. There was another challenge to clear other than to realize the almost impossible pricing as **1,000 yen per gram.** With the acetic acid extraction method developed by Hirosaki University, core protein of proteoglycan could not avoid to be disconnected on the way thus hyaluronic acid was not to be combined. So we could have been successful in extracting **the crude natural proteoglycan**, which was the most difficult challenge to resolve.



## Decomposition of proteoglycan by acetic acid extraction



## Hyaluronic acid is not to be combined!



Moisture retention ability that represents proteoglycan is raised by being combined with hyaluronic acid, so the moisture retention effect will be spoiled when this combined part is lacking.



## The solution was alkaline extraction Natural and pure proteoglycan

After having become independent in 2005, I have started my own study on mass production of proteoglycan by using all of my property. **To make the pricing into 1/300 and to extract proteoglycan in a natural form as it** is without being decomposed by disconnection of core protein, I have tried everything that I could think of and repeated experiments day after day.

In the end I could reach at a **method which is totally opposite method to the acetic acid extraction**, the alkaline extraction. I was not in pursuit of the theory itself. All the researchers were thinking then that nobody would use caustic soda when to protect protein. But I had an intuition that it would be successful in some way.

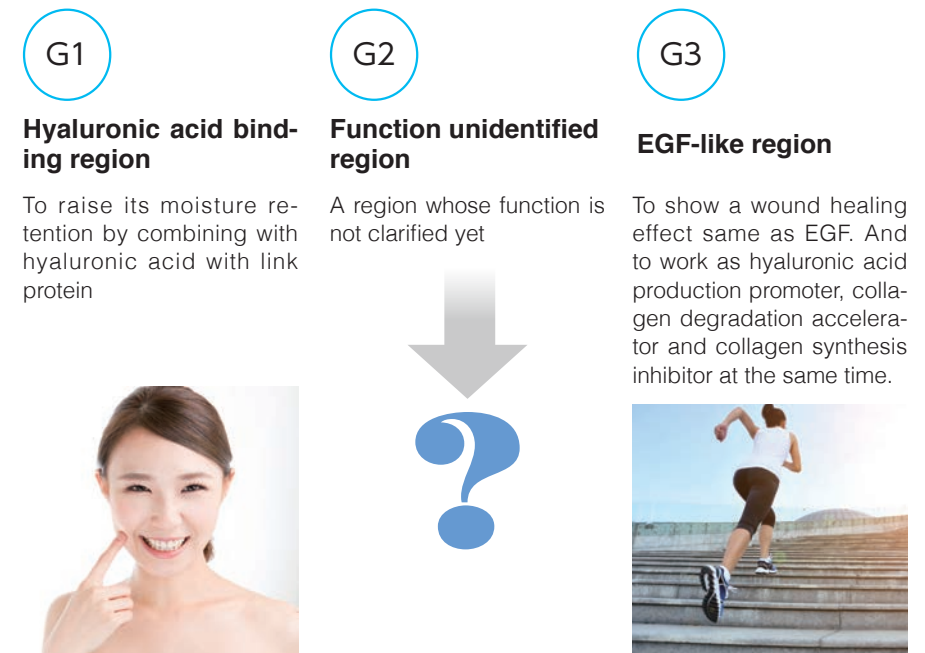
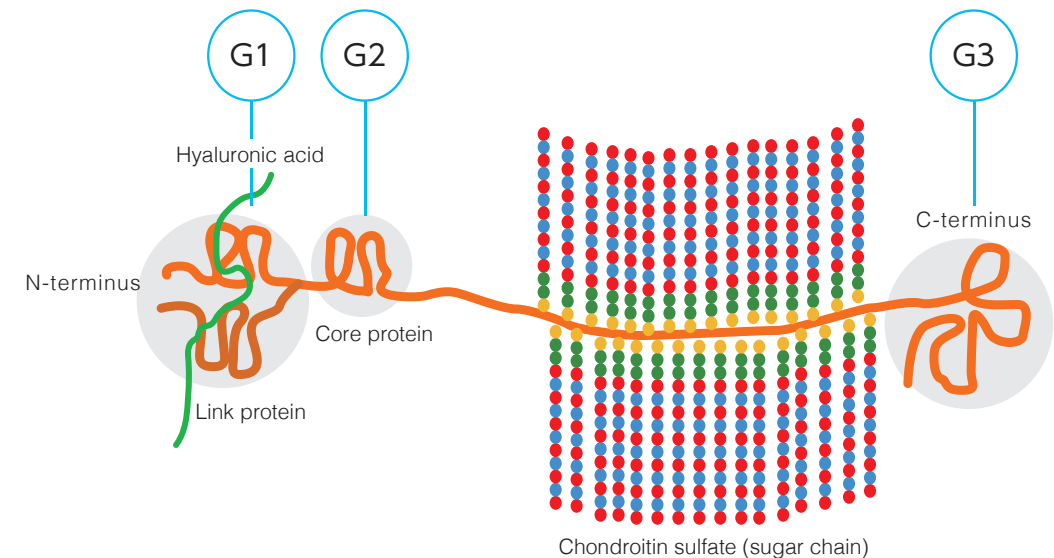
Caustic soda is inexpensive and it will not disconnect core protein in proteoglycan, but the requirement is quite severe. If the factors as temperature, concentration and time are changed even slightly, its extraction rate would change a lot. So **I had to repeat experiments more than 1,000 times**.

The budget was nearly to be used up, and I was just thinking of giving it up if I could not be successful in that last experiment, where the miracle occurred. I had finally found an ideal extraction method of proteoglycan that I had long pursued for, which to keep its purity at 90% and above, its price at less than 1,000 yen per gram, not to be disconnected on the way.

Soon after this miracle happened, I had named this proteoglycan as **natural proteoglycan** and applied for patent.



### Structure and functionality of natural proteoglycan





## Establishment of LPT (Leave Protein Technology) Purity 90% and above, a miracle compound

I was so lucky enough to establish **LPT (Leave Protein Technology) by alkaline extraction** only after 6 months from starting to study on my own while there are tons of scientists who reach their goal throughout their lifetimes.



Natural proteoglycan got into the news and won many big honors as **the Monozukuri Nippon Grand Award "Prime Minister's Award"**.

As you may know, human body consists of cells and they are supported by the extracellular matrix. And the most important worker of them all is proteoglycan. To broadly send it out into the world is to contribute to medical science as well as human healthcare.

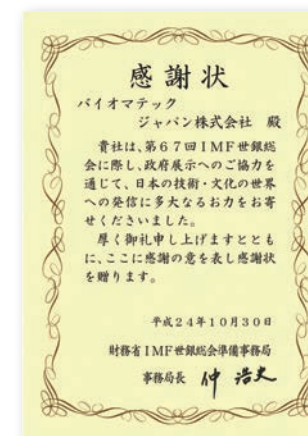
But still, there are so many **poor-quality ingredients that are named as proteoglycan**. One with additional agents such as digestion resistant dextrin or cartilage glint into powder are even named as proteoglycan to be used in health foods or cosmetics. Their quantity written on the package is nothing to be relied on.

In such a society, it's not yet a good timing for me to retire.

I commit to keep developing crude natural ingredients not only proteoglycan but other useful ones to activate self-healing power of human beings.



In 2012, I won the Monozukuri Nippon Grand Award "Prime Minister's Award". I was at the award ceremony and was given a chance to give explanation about proteoglycan to the then prime minister Mr. Noda at the prime minister's official residence.



In 2012, the manufacturing process of natural proteoglycan has been recommended and exhibited at the government-sponsored exhibition as a leading technology in Japan.



In 2008, proteoglycan was patented in Japan



The Biomatec Japan company office building at the Kushiro industrial park in Kushiro, which was newly completed in July, 2015

## The merits of natural proteoglycan

### 1.Safe and reliable ingredients

There is no problem for ingestion. All the reagents used in the extraction and refining process are approved as additives. All the rooms in the factory are clean, whose product control and quality control meets the GMP standard. Salmons as an ingredient are all captured in Hokkaido. We are not using any of the cultured salmons that are administered antibiotics.

### 2.Side effects risk free

We have got no report for allergies neither side effects so far.

### 3.High purity

Percentage of proteoglycan in solid content is 85% and above, and the total percentage of all others as protein or fats is 15% or below.

### 4.Non-heat manufacturing

No heat treatment is done in the whole process. Since proteoglycan contains protein, it will lose its original function by being heated with its protein denatured or decomposed.

### 5.Additives free

No additive as extending agent or preservative is used in our product.

# Natural proteoglycan Mechanism of the miracle compound

Effects on beauty/Effects on health



## Regeneration of the fresh young skin with the same kind of effect as EGF

To promote regeneration of cells by its own effect

EGF (Epidermal Growth Factor) is a kind of protein exists in human skin, which is discovered by Dr. Stanley Cohen, a Nobel-prize winner chemist. It is unveiled not only to regulate the cell function but also to promote their growth, so its **effect as a beauty ingredient is remarked**.

EGF secretion drastically declines after 20s as human age, and **it declines to nearly half or one-third when we come to 40s**. It leads to cell deterioration which causes skin troubles as drying, hardening, wrinkles or moth patches.

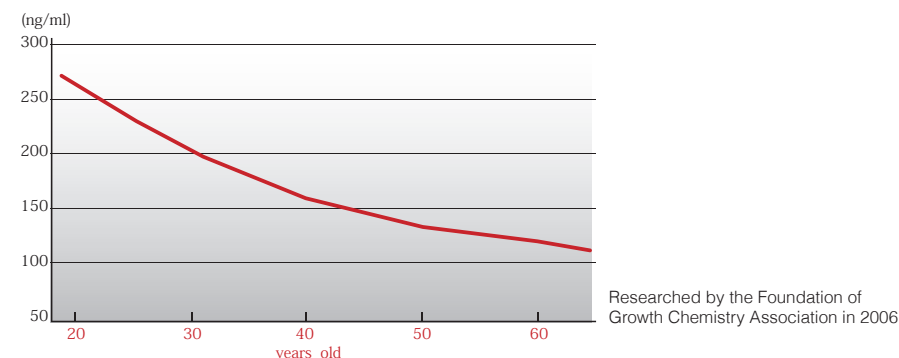
It is clarified that proteoglycan has a same effect as EGF to **promote regeneration of skin cells**. This is the original function that is not with collagen or hyaluronic acid, and moreover, **it promotes production of collagen and hyaluronic acid themselves**, which is the point to be greatly remarked as a material of aging care cosmetics.

To supplement function of EGF which is getting less as we age, as well as to activate and reinforce hyaluronic acid and collagen. Both as a control tower and a star player of extracellular matrix, proteoglycan is a fundamental material **to activate cells to keep themselves fresh and young**.

Range of its application is not only for beauty, but it is also kept studied to be used for regenerative medicine **to cover losses of tissues in the body**.

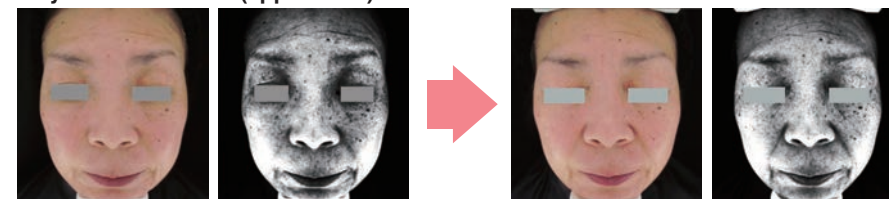


## EGF decrease that accompanies the aging process



## Test examples of beautiful skin regeneration by natural proteoglycan

### 52 years old woman (application)



#### At the first measurement

#### 12 weeks after starting application

52 years old woman	Moisture	Sebum capacity	Visible pore amount	Complexion	moth patches
Before	57	2	1814	809	23
12 weeks later	80	29	1668	880	19

Applied the PG beauty fluid with high purity proteoglycan (PG) 1% and methyl paraben 0.15% as a preservative two times a day every morning and night after face washing for continuous 12 weeks, and measured her skin 2 times, before and after application at the third party organization (Otemachi Park Clinic / Chiyoda-ku Tokyo).

### 44 years old woman (ingestion)



#### At the first measurement

#### 12 weeks after starting application

44 years old woman	Moisture	Sebum capacity	Visible pore amount	Complexion	moth patches
Before	62	9	1810	98	16
12 weeks later	71	23	1683	350	16

Drank the PG solution 100ml with high purity proteoglycan 100mg or equivalent two times a day before breakfast and before going to bed for continuous 12 weeks, and measured her skin 2 times, before and after application at the third party organization (Otemachi Park Clinic / Chiyoda-ku Tokyo).



## High water-retention ability beyond hyaluronic acid

Both application and ingestion are OK  
Keep the moisture in skin cells

Suppleness, moisture and dew are foundations of beautiful skin. Skins of babies are 80% made from water. When we become adults, the water decreases to 60-70% and it keeps dipping as we age.

As moisture retention ingredients, hyaluronic acid and chondroitin sulfate are remarked for their high water retaining capacity.

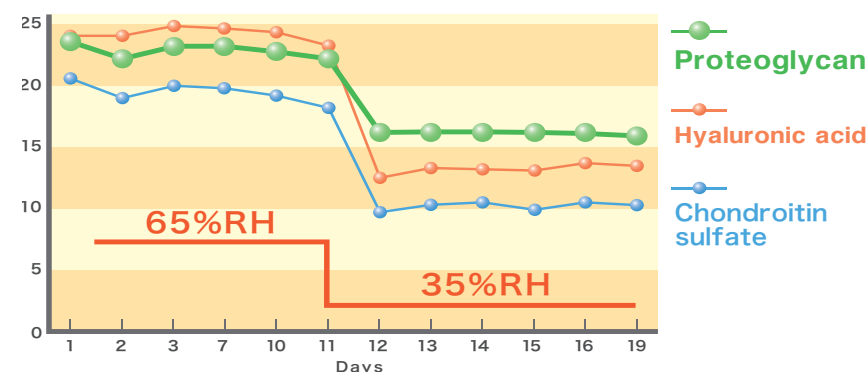
But it is clarified that **proteoglycan exceeds them 30% in the water retaining capacity**. One of the reasons is that hyaluronic acid is easy to be decomposed but proteoglycan is hard to be decomposed as well as hard to be dried by passage of time. Also, hyaluronic acid can normally get a little effect in case of ingestion but **proteoglycan can work both application and ingestion cases**.

And the biggest difference from other ingredients as hyaluronic acid is that proteoglycan works as **to promote genesis of hyaluronic acid and collagen inside skin**.

More than as a simple ingredient that has amazing water-retaining capacity, proteoglycan reinforces other water retention ingredient, which we should call it **a skin trouble savior** from decline of water-retaining capacity or drying by aging.



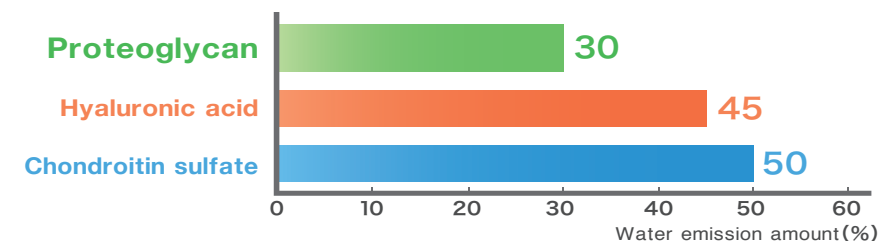
### Comparison of moisture retaining capacities



Comparative test of moisture retaining capacities between natural proteoglycan, commercially available hyaluronic acid and chondroitin sulfate was done.

As a result, under circumstance of relative humidity (RH) 65%, hyaluronic acid was slightly higher in moisture retaining capacity. However, when the relative humidity was forced to be lowered to 35% on the eleventh day, both of the products released water and their weights dipped. But there was a big difference in how their weight dips to prove that the moisture retaining capacities of natural proteoglycan is the highest. So it was clearly shown that natural proteoglycan is the most effective for arid regions, dry seasons and dry skins.

### Comparison of water emission amount





## Getting rid of dry skin/moth patches/wrinkles/loose skin with its anti-inflammatory action

Dissolution of skin worries and troubles to feel anti-aging

When we talk about skin-beautifying effect of natural proteoglycan, we cannot skip to mention about its anti-inflammatory action. There might be someone who doubts its relevancy with skin-beautifying, but actually **skin troubles as acne, dry skin or sunburn is a sort of inflammations.**

**Symptoms of aging as skin wrinkles, moth patches or loose skin are accelerated by cytokine TNF- $\alpha$  (Tumor Necrosis Factor- $\alpha$ ) that causes inflammations.**

TNF- $\alpha$  is also an aggravating factor for patients' conditions as GVHD (Graft-Versus-Host-Disease) that are seen on diabetes, rheumatoid arthritis and marrow transplants.

Proteoglycan not only suppresses function of the cytokine but also activates function of anti-inflammatory cytokine (IL-10) that suppresses inflammations.

It has a **dual effect to suppress inflammations**. So it is expected to be applied not only to skin troubles but also to **prevention of inflammatory diseases and autoimmune disorder.**

Also, sunburn is a skin inflammation that skin pigmentation is caused even after the inflammation stops, and moth patches come out to the skin as we age.

Proteoglycan works not only to suppress inflammations but also **to improve pigmentation**. It is clarified that ingestion of proteoglycan lessened preeminent moth patches.

And cell assay also showed an effect **to control melanin pigment generation** which causes moth patches.

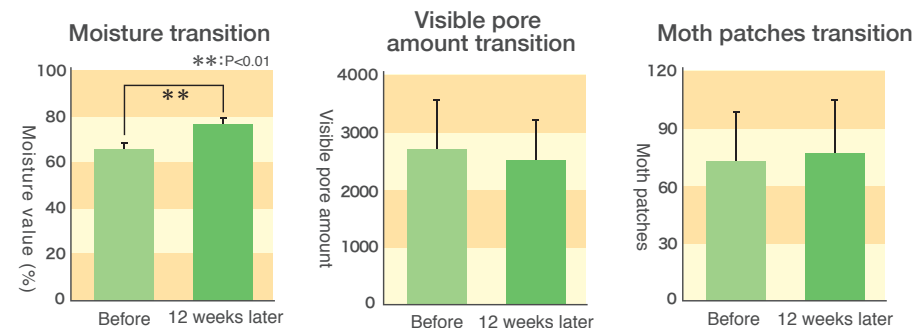
Like this, Proteoglycan not only prevents and restores skin damages but also refreshes and regenerates skin cells themselves back to be young. As **an almighty ingredient for skin anti-aging** that has both symptomatic treatment effect and complete cure effect, proteoglycan is expected to be applied to various products.



## A human study on application of proteoglycan essence

**Target: Healthy 8 women from 40s to 60s**

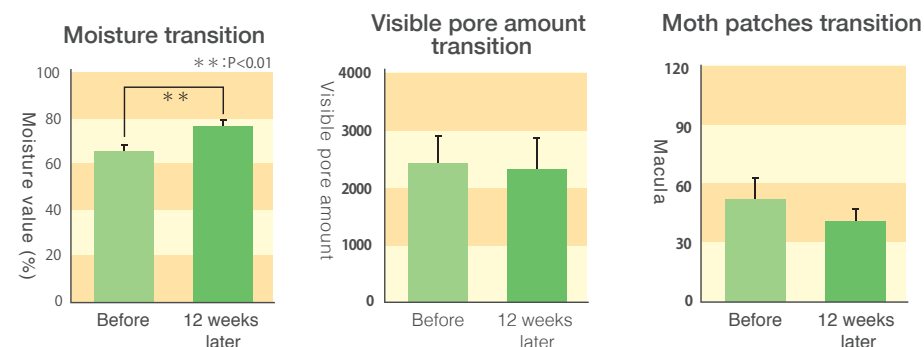
Applied the PG beauty fluid with high purity proteoglycan (PG) 1% and methyl paraben 0.15% as a preservative two times a day every morning and night after face washing for continuous 12 weeks, and measured their skin 2 times, before and after application at the third party organization (Otemachi Park Clinic / Chiyoda-ku Tokyo).



## A human study on ingestion of proteoglycan water solution

**Target: Healthy 6 women from 40s to 60s**

Drank the PG solution 100ml with high purity proteoglycan 100mg or equivalent two times a day before breakfast and before going to bed for continuous 12 weeks, and measured their skin 2 times, before and after application at the third party organization (Otemachi Park Clinic / Chiyoda-ku Tokyo).





## Improvement of obesity/diabetes

The first step to block adult diseases  
Excretion of glucose or fat by chelating

In recent study, it is clarified that fat cells themselves generate several villain factors in relevant to onsets of diseases. It is originally a function to improve overweight and keep proper condition, but as obesity proceeds, these villain factors become too much to come to hurt their own somatic cells. So **obesity is just as somatic cells are in inflammations by being hurt.**

Also, when these villain factors increase in the body, **sensibility against appetite regulation hormone decreases** to invite overeating and obesity proceeds.

Like this insulin activities are deteriorated to **raise risk of diabetes.**

It is clarified in the test on mice by Hirosaki University that **proteoglycan suppresses body weight increase and work on to decrease liver fat.**

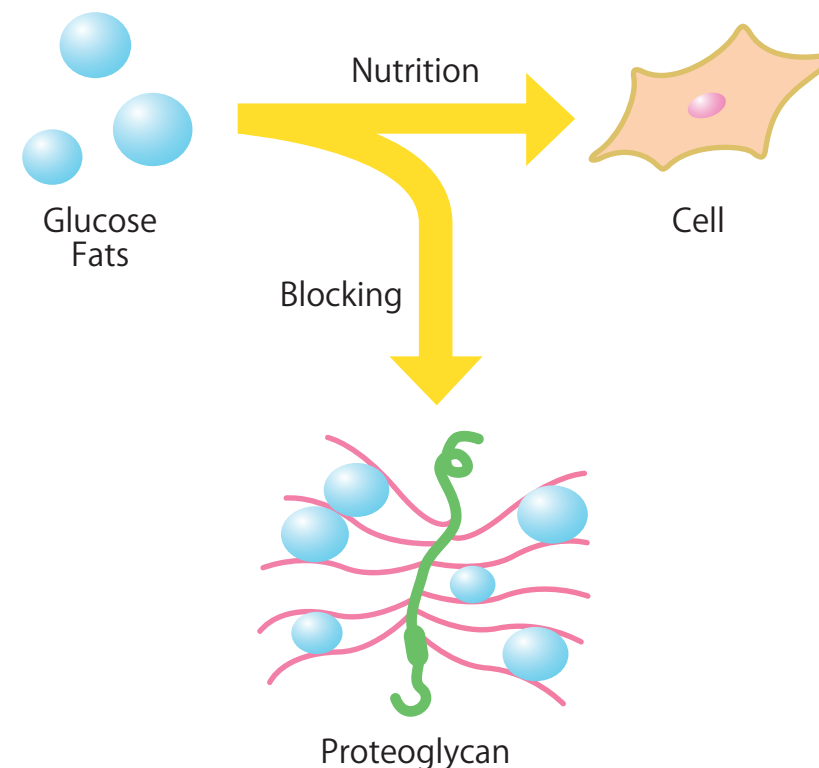
**Proteoglycan works to take extra body fat in and discharge them from bodies.**

Other than this, proteoglycan works to bring the inflammatory cells by getting obese back to be healthy to relieve risk of obesity or diabetes at the base by **taking anti-inflammatory actions** and **suppressing active oxygen generation.**

By having an integral effect as discharging excess fat or body wastes out and suppressing cell inflammations, proteoglycan keeps cells healthy **to prevent adult diseases.**



## Glucose and fats holding capacity of proteoglycan



When proteoglycan is added to glucose or fats, they are held by proteoglycan and blocked to be absorbed from small intestine. By making use of this function, it is thought that a diet food can be developed. Also, as the absorption of glucose and fats are suppressed, a preventive effect on diabetes is expected.



## Resolution for incurable diseases as inflammatory bowel diseases by suppressing excess immune function

Normalizing function of intestinal tract immune cells by making out a good bacteria superior circumstance

It is also found that proteoglycan has an effect against inflammatory bowel diseases as “ulcerative colitis” and “Crohn disease”, the specified diseases as intractable diseases by Ministry of Health, Labor and Welfare.

The cause of inflammatory bowel diseases are not yet clarified, thus their remedies are not established. Moreover, **designated victims of ulcerative colitis in 2012 were 77,073**, and now it reaches 100 thousand people and still the number of patient are increasing year by year.

Against this serious disease, a study group led by Dr. Yoshihara in a surgery team of Hirosaki University clarified an improvement effect of proteoglycan in an experiment on mice.

Its mechanism has not been clarified yet but against inflammatory reactions that causes inflammatory bowel diseases, **proteoglycan works to normalize the function of intestinal tract immune cells by changing circumstance inside the intestines to be good bacteria superior.**

By suppressing excess inflammations, it is thought that proteoglycan influences the whole body immune system to work to keep the constancy of a living body.

Proteoglycan is confirmed **to be absorbed from intestinal tract without being processed.**

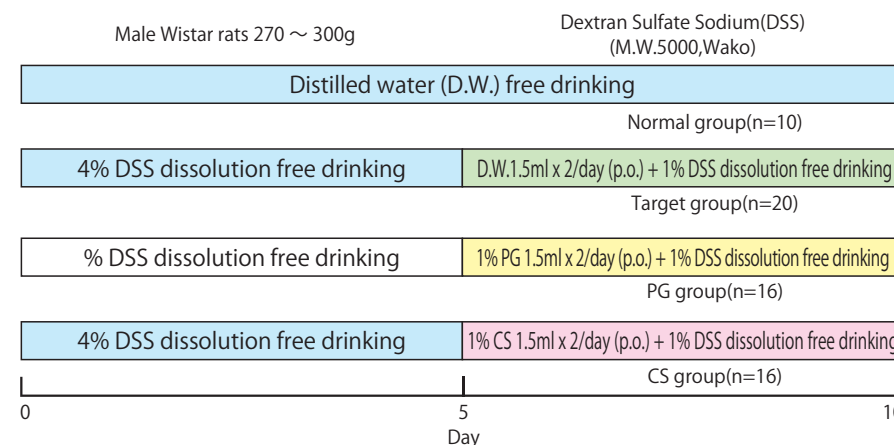
Especially, absorptivity in jejunum as a part of small intestine is high to be delivered not only inside intestine but all over the body soon. Proteoglycan is expected to adjust immune function of the whole body to resolve various incurable diseases other than inflammatory bowel diseases.



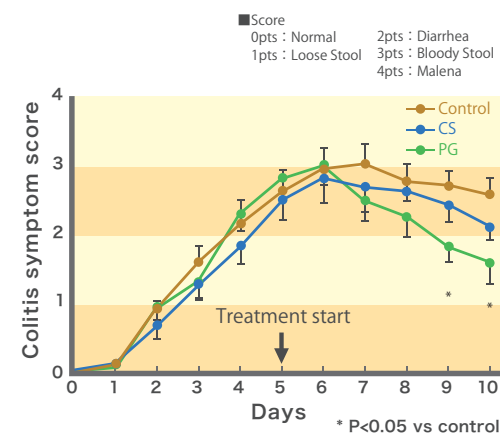
## Application of proteoglycan on inflammatory bowel diseases

Hirosaki University, the second surgery and the first biochemistry (Shuichi Yoshiwara, Misato Ota, Kaoru Kojima, Keiichi Takagaki, Mutsuo Sasaki)

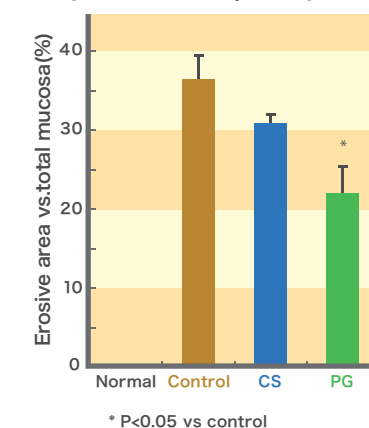
### Effect of proteoglycan (PG) in the DSS-induced enteritis model



### bleeding/diarrheal symptoms transition



### Effect of proteoglycan (PG) against mucosal injuries by DSS



### Conclusion

- Against the DSS-induced enteritis model, a treatment acceleration effect on enteritis was indicated with bleeding and diarrheal symptoms, hematological observation and histopathologic observation being improved by proteoglycan oral administration.
- n-butyric acid concentration within colon was significantly increased by proteoglycan oral administration.
- From results above, it is indicated that the curative effect of proteoglycan against the DSS-induced enteritis model is possible to be brought about by increase of n-butyric acid.



## Improvement of arthralgia by regenerating cartilages Block of osteoarthritis

Regeneration of cartilaginous tissues by suppressing inflammations of arthralgia

Osteoarthritis arises with exhausted cartilage by aging and the like, which leads to arthritis or deformation to cause pain. **Ten million people above 50 years old experienced knee pain by osteoarthritis of the knee**, and almost all the people by 80 years old may be influenced to some extent.

Once the articular cartilages are exhausted, it is hard to be recovered that triggers stresses in daily behaviors, and neglecting them is said to lead to an increase of the death rate.

Proteoglycan is an important ingredient to form cartilages together with collagen and hyaluronic acid that has high water retaining capacity to play a role as **an articular cushion** as elasticity or shock absorption. To begin with, osteoarthritis emerges being caused by regenerative faculty deterioration after proteoglycan decreases as we age. And damage of cartilages breaks collagen fibers and denatures proteoglycan.

It is clarified that by intake of this proteoglycan, precursor cells of cartilages increase **to regenerate cartilages and then pains are alleviated by anti-inflammatory action to improve osteoarthritis**.

Proteoglycan is expected to have effect to **fundamentally improve articular disorders** because **it promotes metabolism of cartilages itself**, which is said to be impossible for hyaluronic acid or collagen.



## Application of cartilage-derived proteoglycan for restoration of articular cartilage

### Purpose

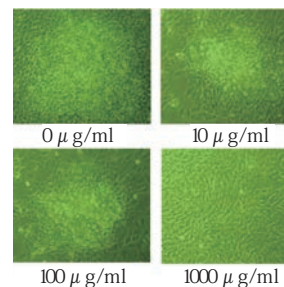
To examine if cartilage-derived proteoglycan can be a material to promote restoration of articular cartilage or not

### Steps

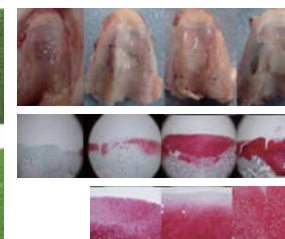
1. Monolayer culture of rabbit cartilage cells on a proteoglycan coated culture dish
2. Three-dimensional culture of rabbit cartilage cells with proteoglycan contained atelocollagen gel
3. Transplantation of proteoglycan contained atelocollagen gel including rabbit cartilage cells for deficiency of rabbit thighbone condylar cartilages
4. Transplantation of proteoglycan collagen sponge for deficiency of rabbit thighbone condylar cartilages

### Result

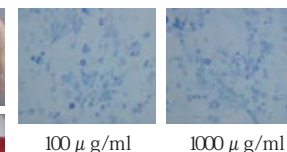
With monolayer culture, cartilage cells aggregate formation enhancement was seen.



With three-dimensional culture, cartilage cells surrounding glucosaminoglycan accumulation promotion and aggrecan revelation promotion were seen.



With gel transplantation including cartilage cells, stainability of recovered cartilages in 100 µg/ml group was better than other groups.



control 0mg/ml 100 1000

### Summary

- Depending on proteoglycan concentration, differences between cartilage cells condensation formation, aggrecan gene revelation and recovery of cartilage deficient part were seen.
- Proteoglycan has a function to suppress cell adhesion, which may have influenced.
- It is possible that proteoglycan itself controlled cartilage cells increase or differentiation.
- Detailed action mechanism is not yet clear, but it will be clarified in future studies.
- Depending on the usage, proteoglycan has a possibility to be a useful medical material future studies.



## Suppression growth of cancer cells by proteoglycan

Attacking cancer cells  
by activating NK cells

Cancer cells spread by performing angiogenesis (new blood vessel branches off from the existing one and structures a vasoganglion). It is clarified that proteoglycan has a function **to block this angiogenesis of cancer cells** to suppress their growth.

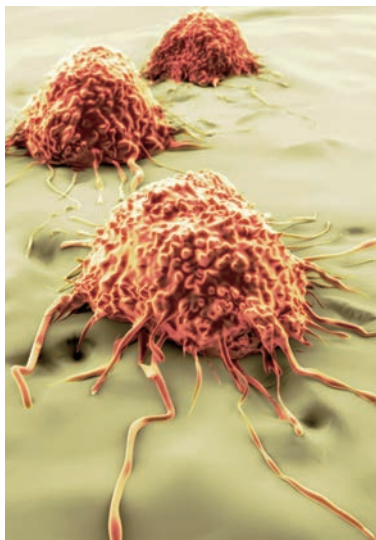
Midkine which is a sort of growth factors is a substance to promote transfer and survive of cancer cells. In various cancers as **esophageal cancer, stomach cancer, large bowel cancer, liver cancer, pancreatic cancer, thyroid cancer, lung cancer, breast cancer, bladder cancer, uterine cancer, ovarian cancer or prostatic cancer**, increased midkine expression is confirmed with about 80% of probability.

Glucosaminoglycan contained in proteoglycan **suppresses transfer and survive of cancer cells by combining with this midkine.**

Also, oral administration of proteoglycan **blocks function of a substance which is called metal proteinase which is generated when cancer transfers.**

By these two functions, proteoglycan prevents spread and expansion of cancer by blocking angiogenesis of cancer cells.

Moreover, a test result is announced that oral administration of natural proteoglycan **activates NK cells which are natural immunity factor to work against tumor cells** or viral infection cells. NK cells are the main natural immunity capacity to attack a newly produced cancer cells to lead them to be eliminated. This function is also greatly expected from the viewpoint of preventive medicine.



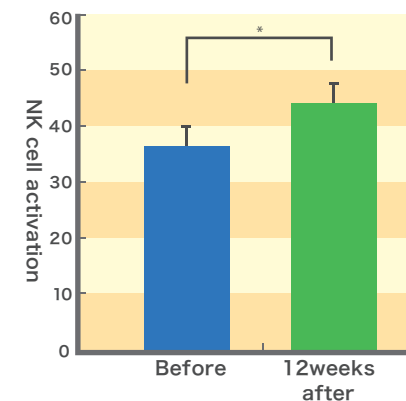
## NK cell activation in human blood increase by proteoglycan intake

### Test summary

Target: Healthy 6 women from 40s to 60s.

Steps:

Drank the PG solution 100ml with high purity proteoglycan 100mg or equivalent two times a day before breakfast and before going to bed for continuous 12 weeks, and measured their blood 2 times before and after ingestion at the third party organization (Otemachi Park Clinic/Chiyoda-ku Tokyo)



Before and after drinking, statistically superior increase in NKcell activation was seen.

## Transition before and after medication of proteoglycan (100mg x 2/day, 12 weeks)

Applicant No.	Age	NK activation		
		Before	after	Δ%
1	61	46	46	100
2	63	27	45	167
3	61	21	32	152
4	42	46	51	111
5	43	23	41	178
6	47	31	36	116
7	54	42	52	124
8	58	51	55	108
9	55	41	38	93

## Definition of proteoglycan

There is no clear definition of proteoglycan, but according to "The Biochemical Dictionary", it is explained as a generic name of covalent bond compound of glucosaminoglycan (mucopolysaccharide) and protein, which used to be called as mucopolysaccharide-protein in old times.

Generally, proteoglycan should be a generic name of complex carbohydrate that several to tens of glucosaminoglycan (sugar chain) are combined to a core protein.

Depending on sorts that compose glucosaminoglycan (mucopolysaccharide, GAG), there exists several different types of sugar chain. Proteoglycan is also classified depending on the sorts of sugar chain.

Natural proteoglycan is a sort that is called chondroitin sulfate proteoglycan.

**Natural proteoglycan is a substance that approaches cells themselves to work on the root that causes various symptoms of diseases**

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# From proteoglycan to natural proteoglycan, the dramatic evolution

## ● Purity 90%

Extraction purity has been raised from about 20% of the total amount to 90%

## ● Extraction time for 1.5 hours

The extraction time has been shortened from wholly 3 days to 1 hour and a half

## ● Cost 1/20

The alkaline extraction technology has decreased the cost to 1/20

## ● Selling price 1/300

Development of LPT and the mass production effect has realized its selling price to 1/300

## ● LPT (Leave Protein Technology)

By clearing the difficulty in the acetic acid extraction process, proteoglycan extraction in its native form has been realized.

## ● The Monozukuri Nippon Grand Award “Prime Minister’s Award”

Having won the Monozukuri Nippon Grand Award “Prime Minister’s Award”

