

# Nahlsgen®

## Maintains the skin's natural youthfulness.

It makes your own cells produce biological substances which make you beautiful.

## お肌本来の若さを保つ！

あなたを美しくする  
あなただけの細胞からつくりだす。  
それが”ナールスゲン®”



# What is Nahlsgen® ?

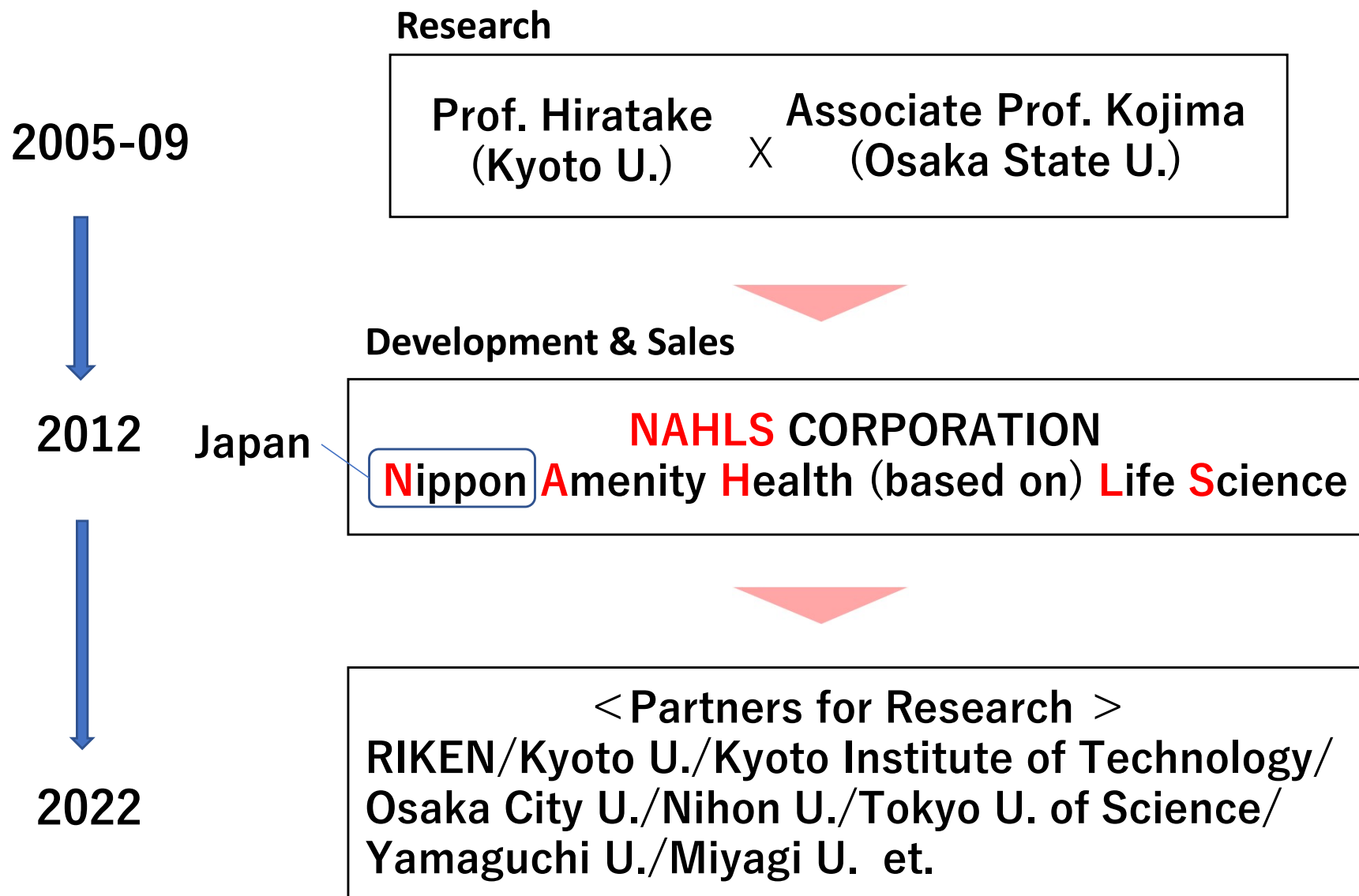
**It makes your skin beautiful and healthier  
from the inside**

**NAHLS CORPORATION**

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# History



## Our Team

### **Kazuo Matsumoto, Ph. D**

- Chairman
- Former director and managing executive officer of Mitsubishi Tanabe Pharma Corp.



### **Motoji Kawasaki, Ph. D**

- President and CEO
- Former R&D manager of Sumitomo Pharma Co., Ltd.



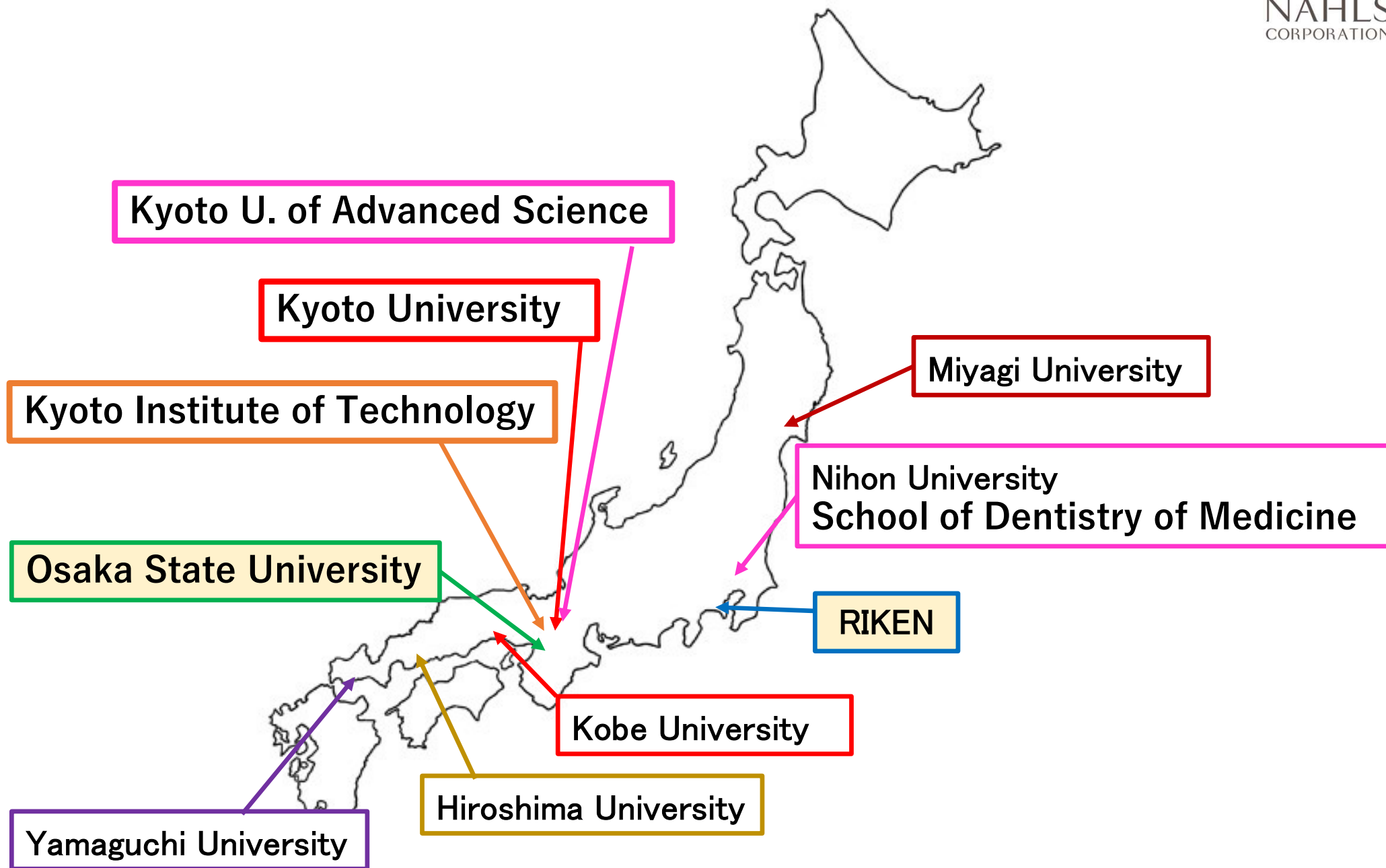
### **Ryuzo Yoshioka, Ph. D**

- Chief Technology Officer
- Former R&D of Mitsubishi Tanabe Pharma Cor.



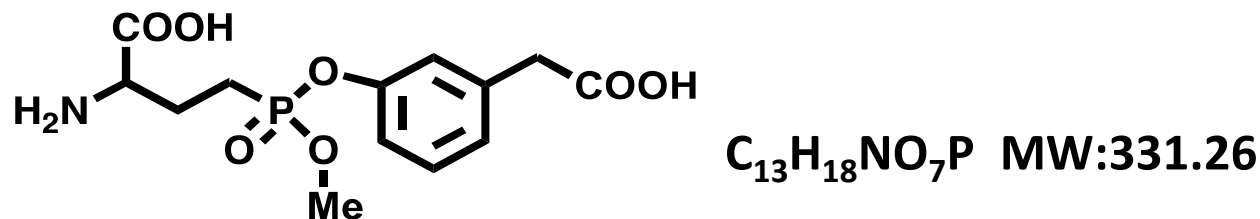
## 5. Research partners

# Research Partners



## Nahlsgen Information

- Chemical structure (Chemically synthesized compound)



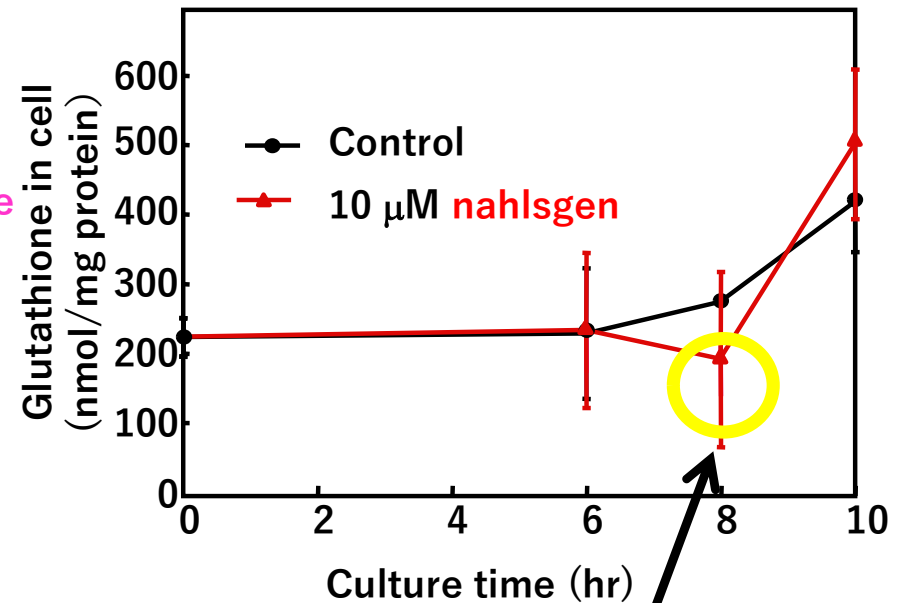
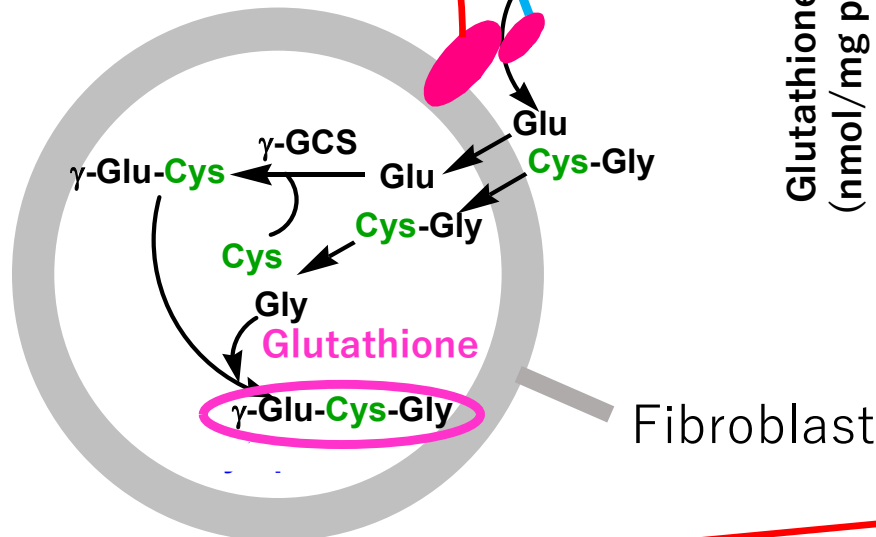
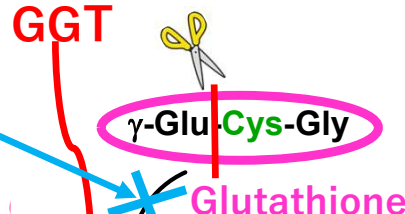
- ナールスゲン®/Nahlsgem® (Sep 2011 : Trade mark registration )
- INCI:  
Methyl Carboxymethylphenyl  
Aminocarboxypropylphosphonate  
China INCI: In process of preparation for application
- Safety test (human monitor test/3 month) OK!  
Stability test (1% 1,3-BG solution/ 4°C/48 weeks) OK!

# Nahlsngen as GGT Inhibitor

What is GGT Inhibitor?

Gamma-Glutamyltranspeptidase

Nahlsngen



Glutathione  $\downarrow$   
(in Fibroblast)

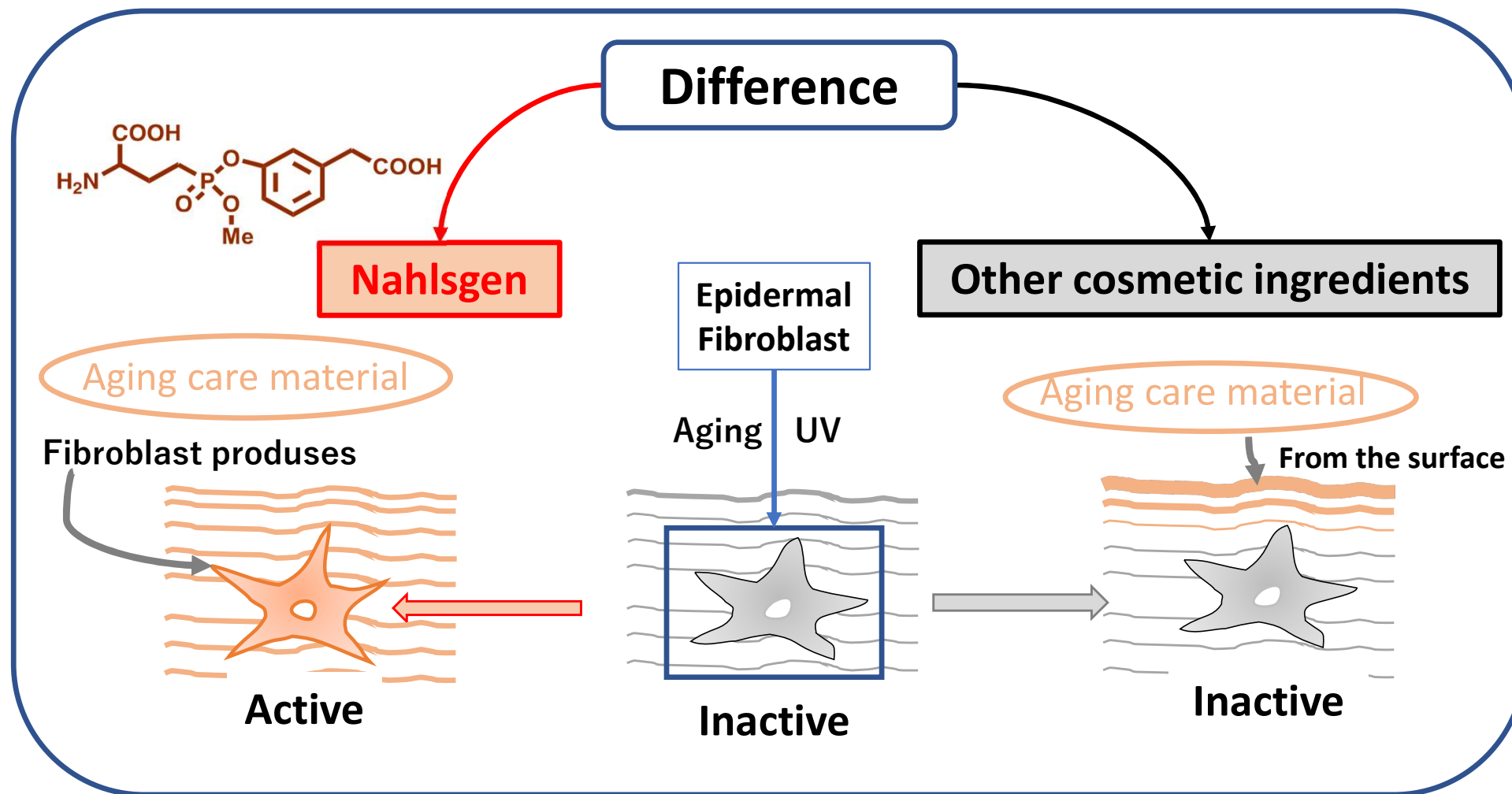
ROS  $\uparrow$

TGF- $\beta$  expression  $\uparrow$

Collagen production  $\uparrow$

Nahlsngen reminds cells of original vitality by giving them light oxidative stress.

# Comparison of **Nahlsigen** with other Conventional aging care cosmetic ingredients



## 6. Nahlsngen's action on skin

**Collagen • Elastin • HSP**

**Hyaluronic acid**

**Glutathione**

**Keratinocyte**

**Loricrin • Keratin 10**

**Wound healing promotion factors**

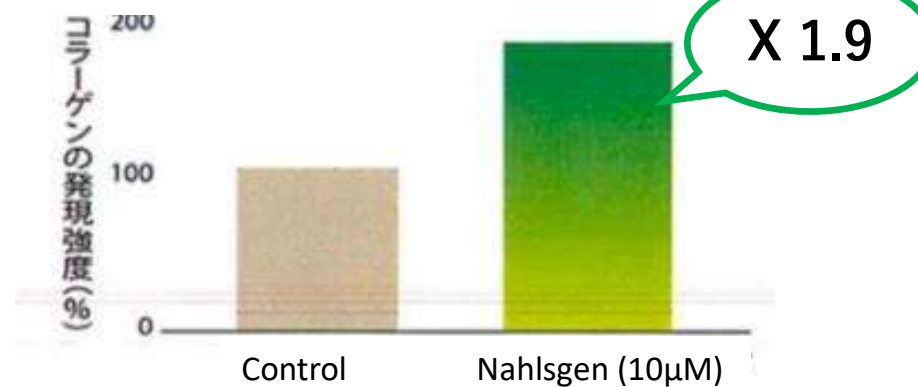
**Melanin**

## 6. Nahlsngen's action on skin

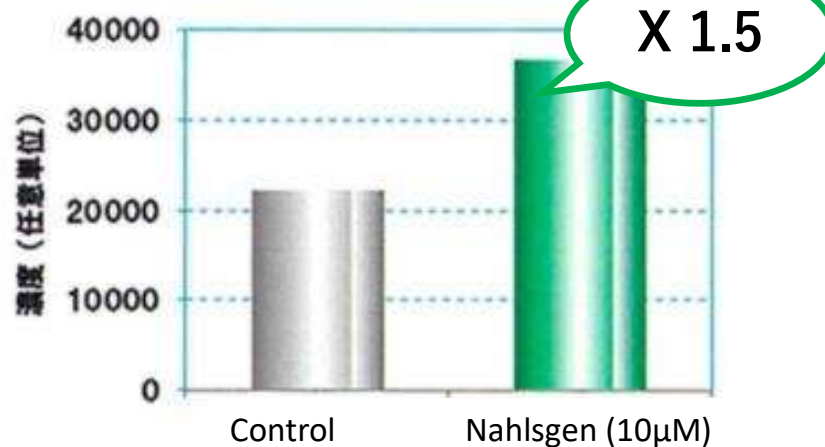
# Collagen • Elastin • HSP

■ In vitro Study

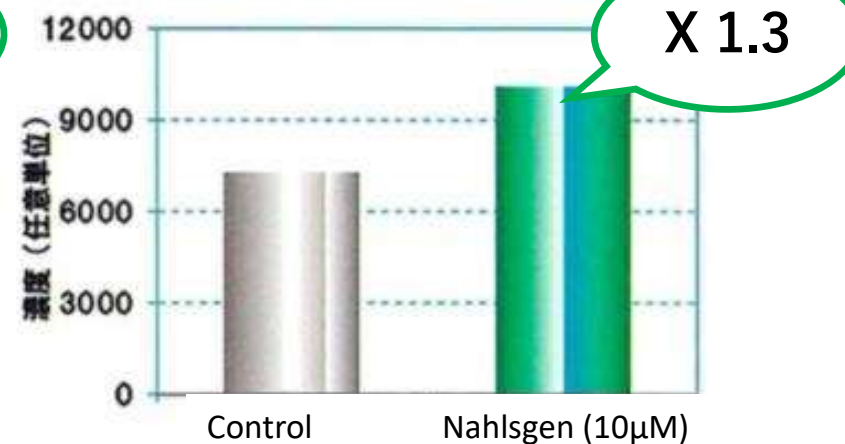
## Collagen



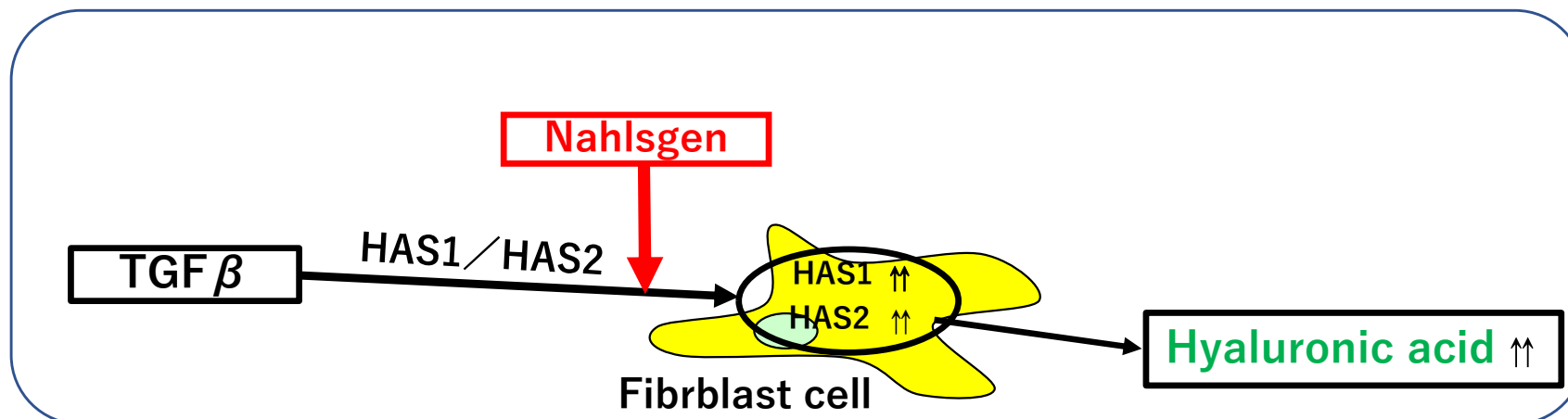
## Elastin



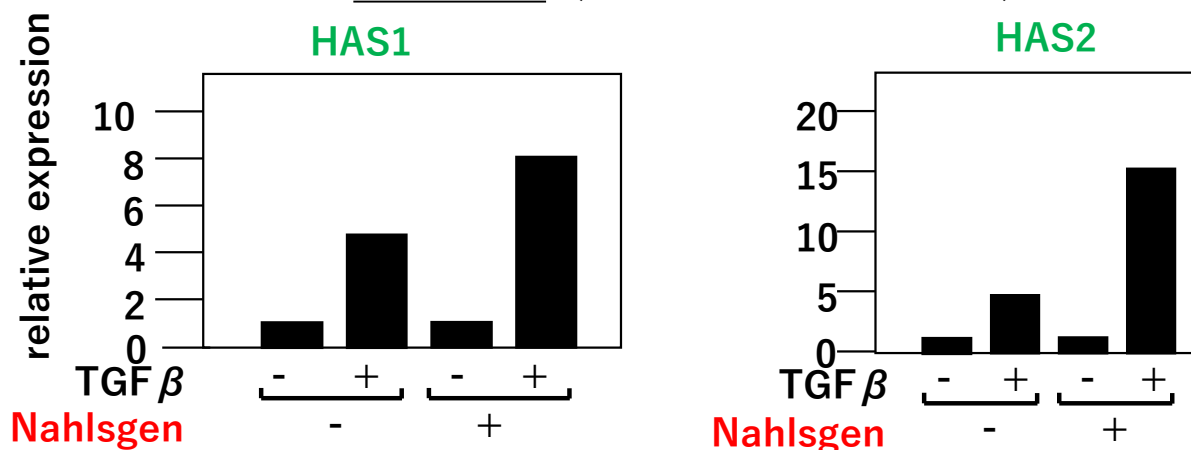
## HSP47



# Hyaluronic acid (1)



RNA Level (Real time PCR method)

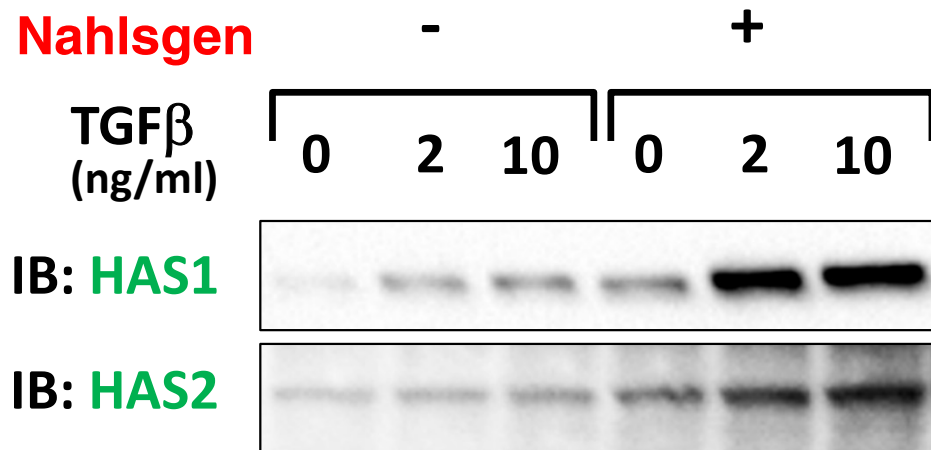


**Nahlsngen** reinforces **hyaluronic acid** production by reinforcing production of **HAS1** and **HAS2** with TGF β synergistically.

# Hyaluronic acid (2)

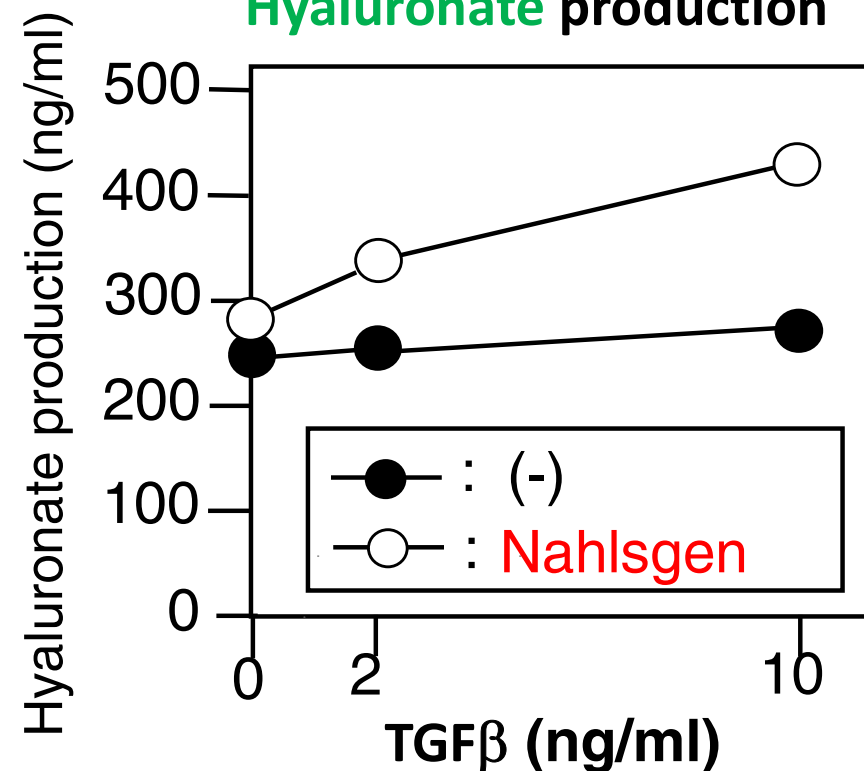
## western blotting

Protein amount of **HAS1/HAS2**



## ELISA method

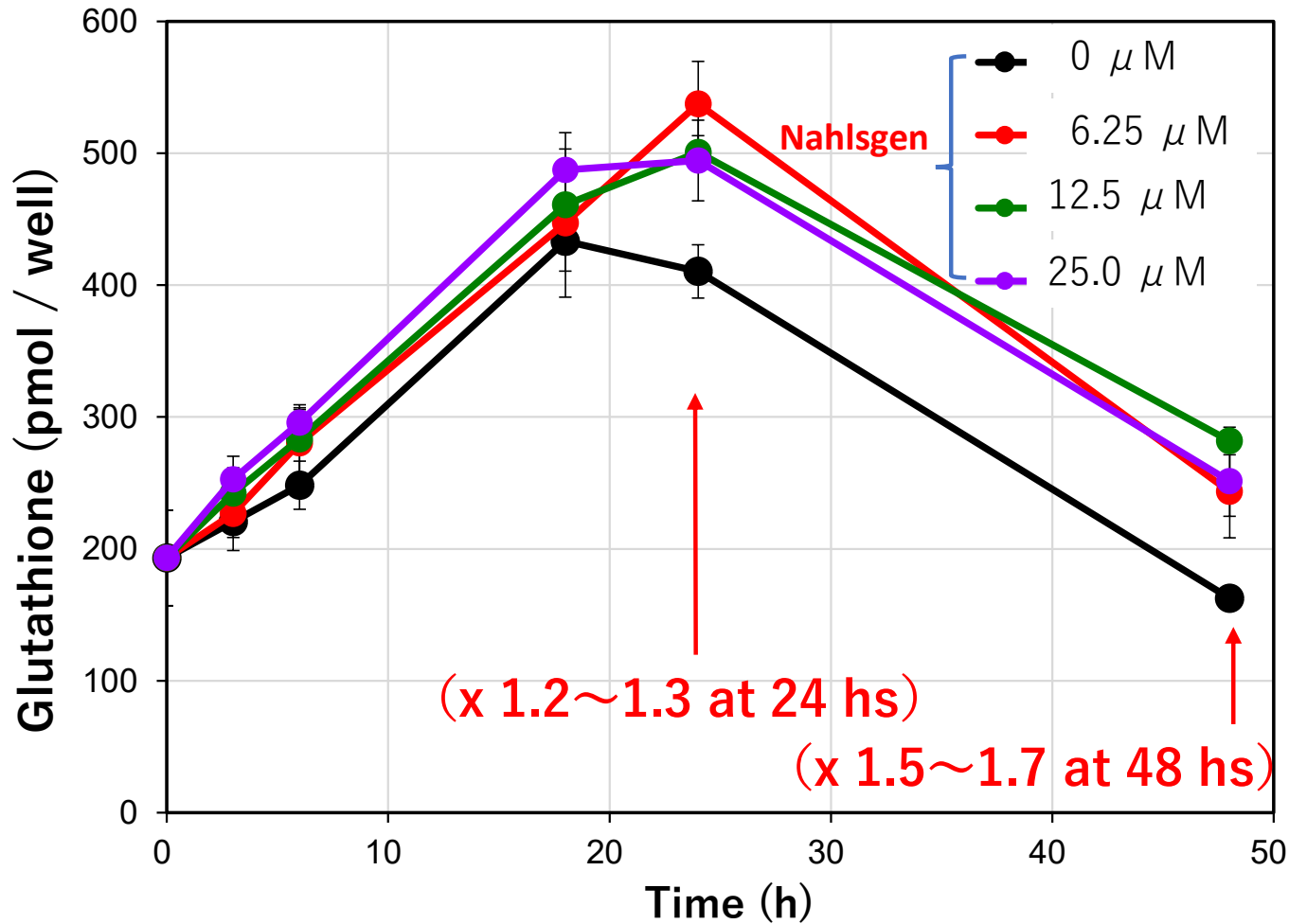
**Hyaluronate production**



**Nahlsngen** and TGFβ increase **HAS1** and **HAS2** protein levels and **hyaluronic acid** production

## 6. Nahlsgen's action on skin

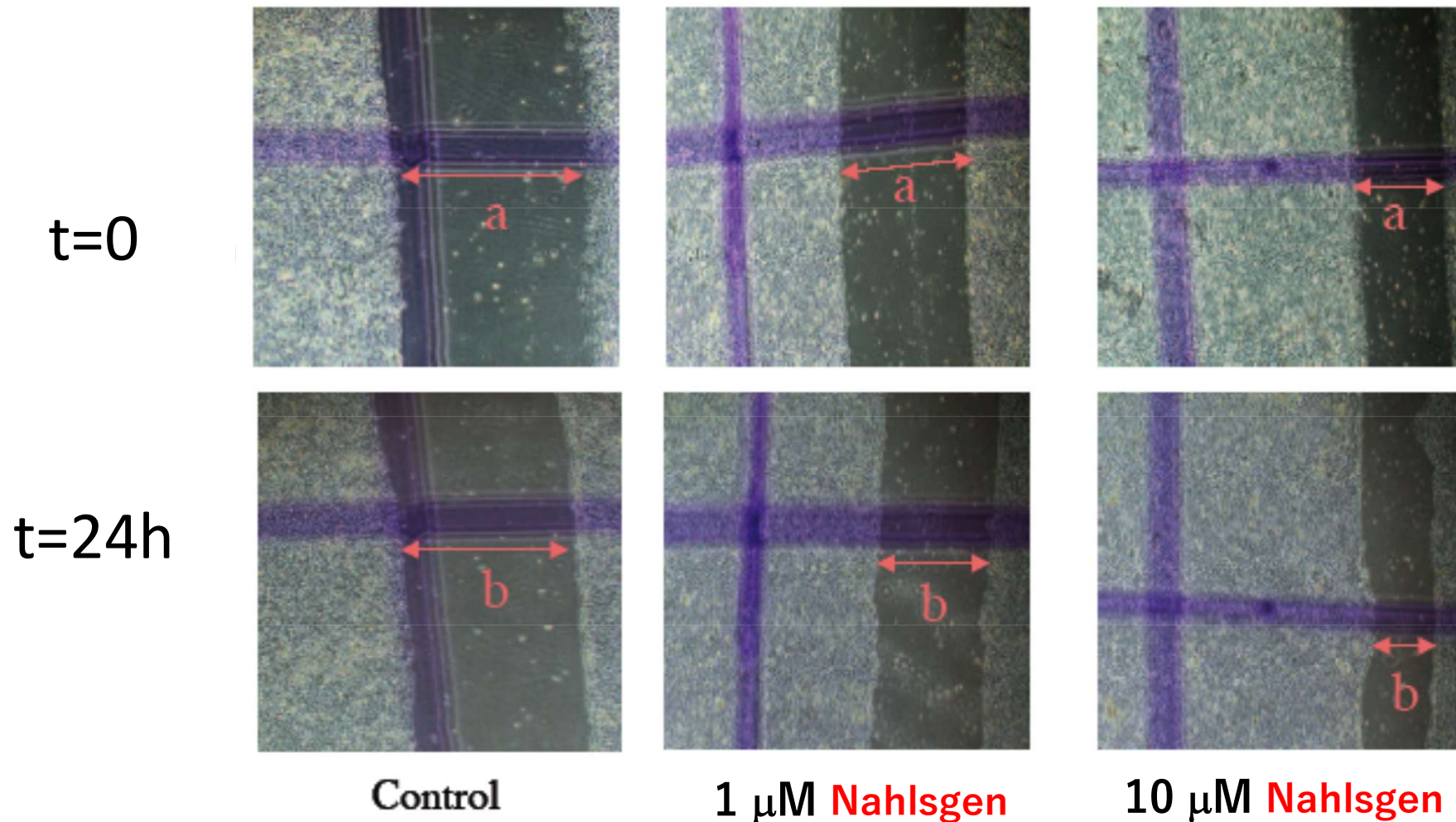
# Glutathione



**Nahlsgen reinforces glutathione production.**

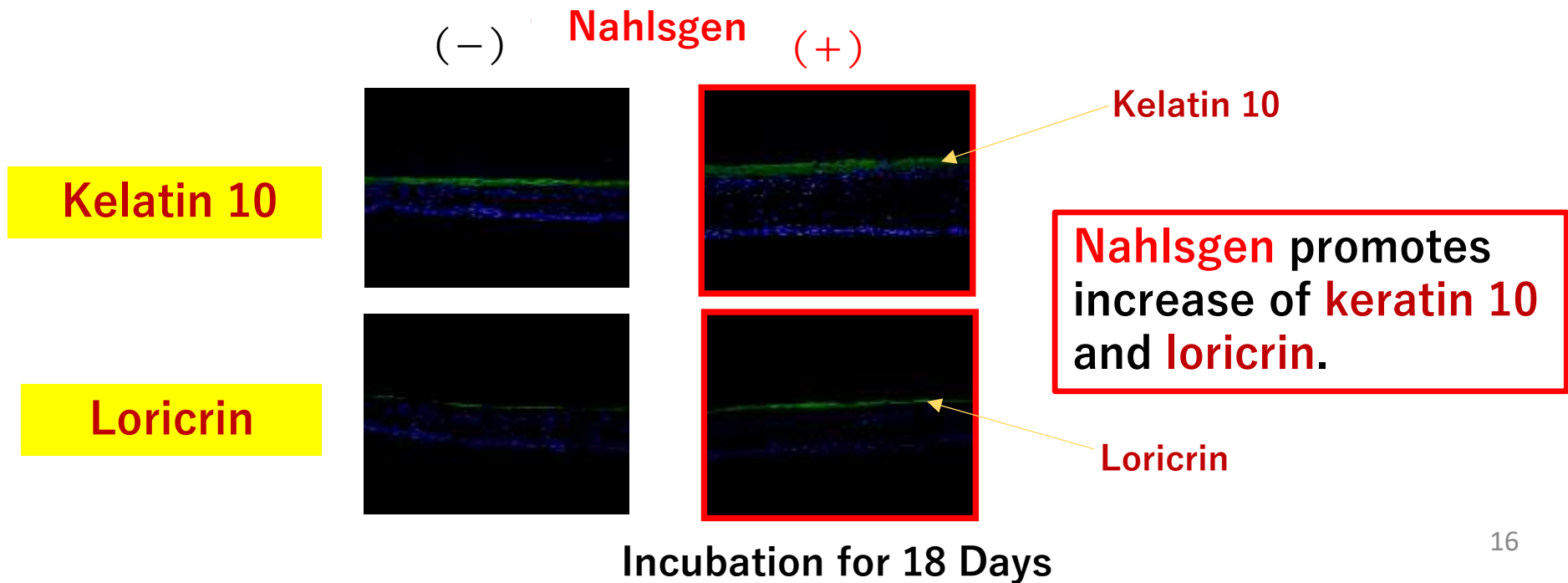
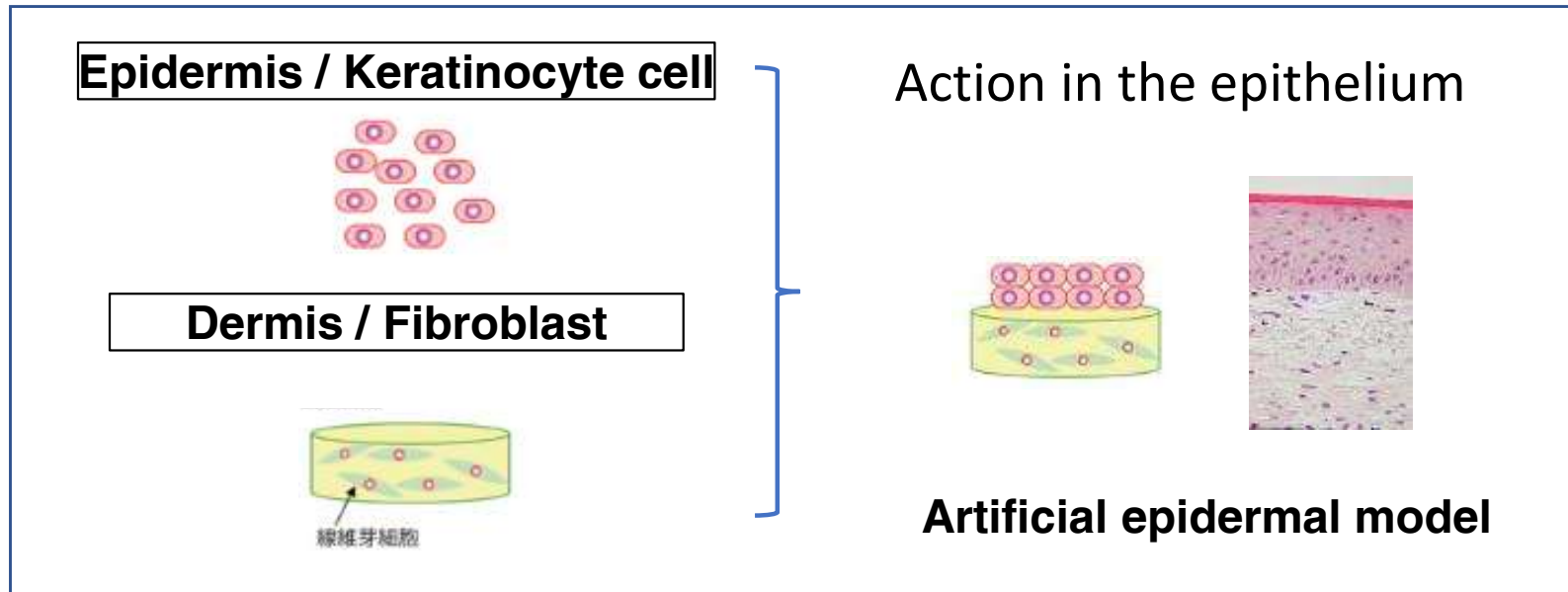
## 6. Nahlsgen's action on skin

# Keratinocyte

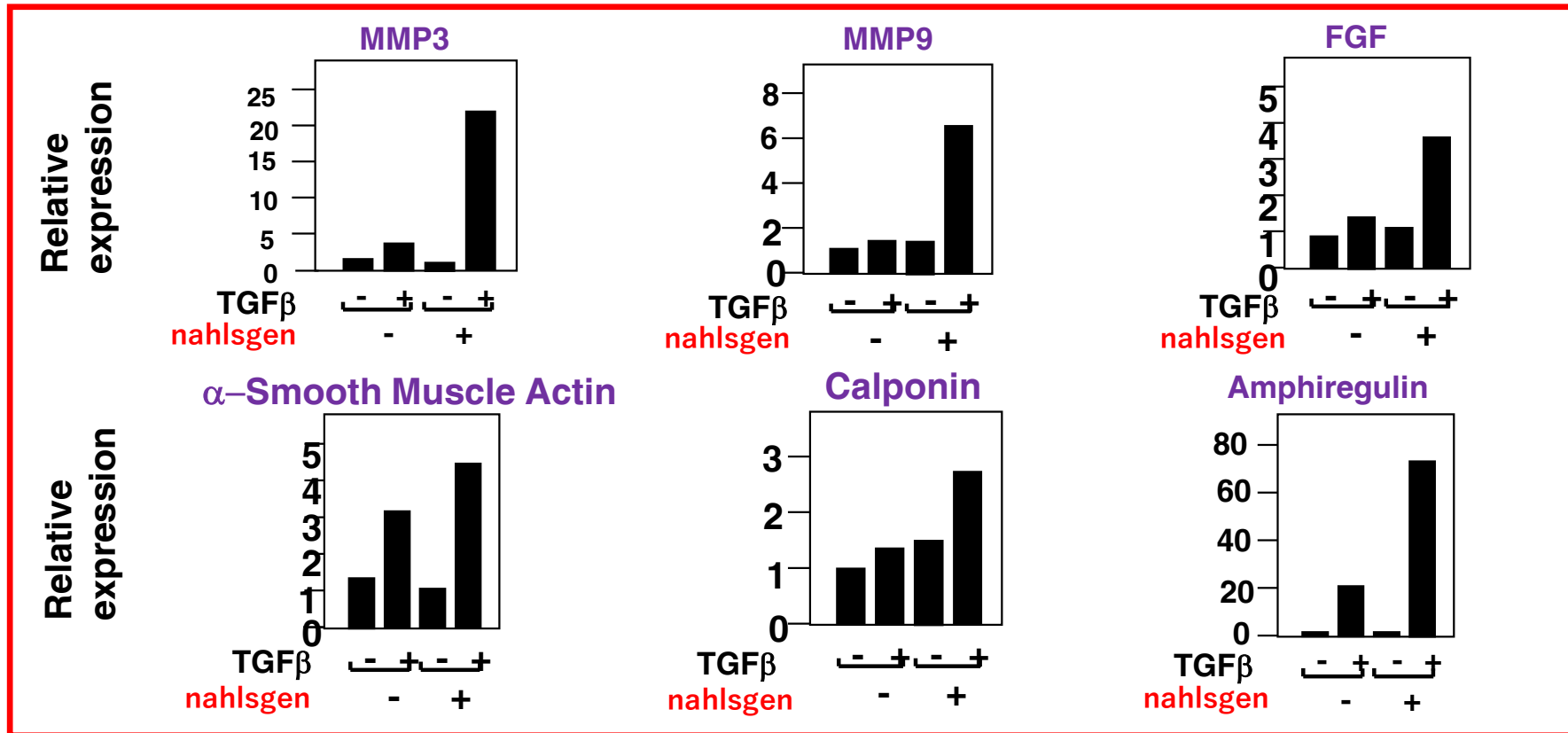


**Nahlsgen** promotes migration and increase of the human **keratinocyte** cells.

# Loricrin • Kelatin 10



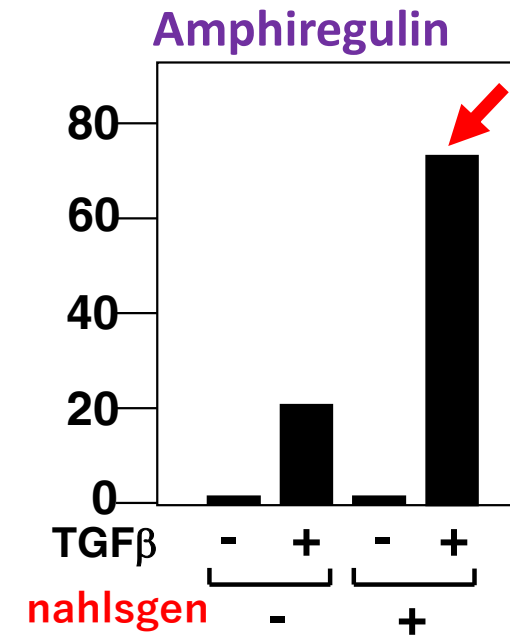
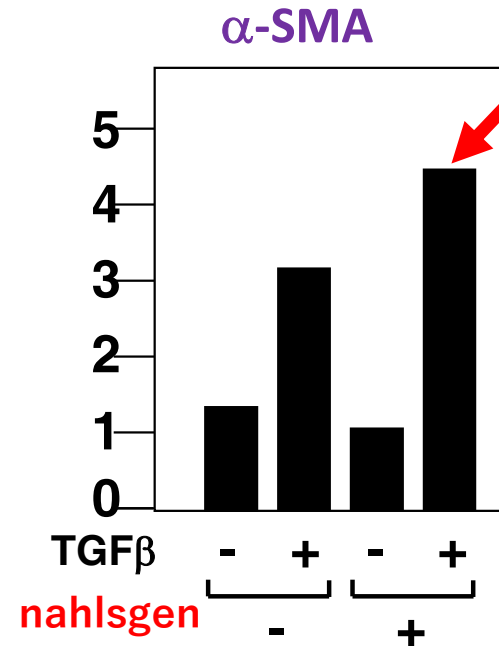
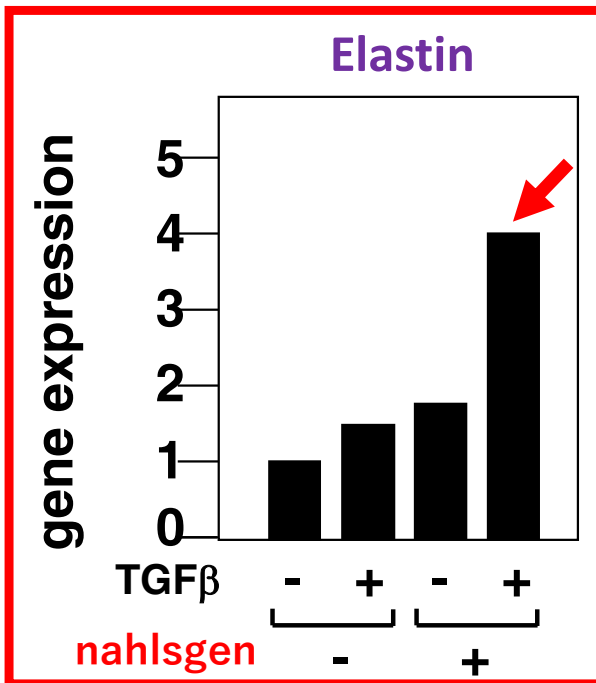
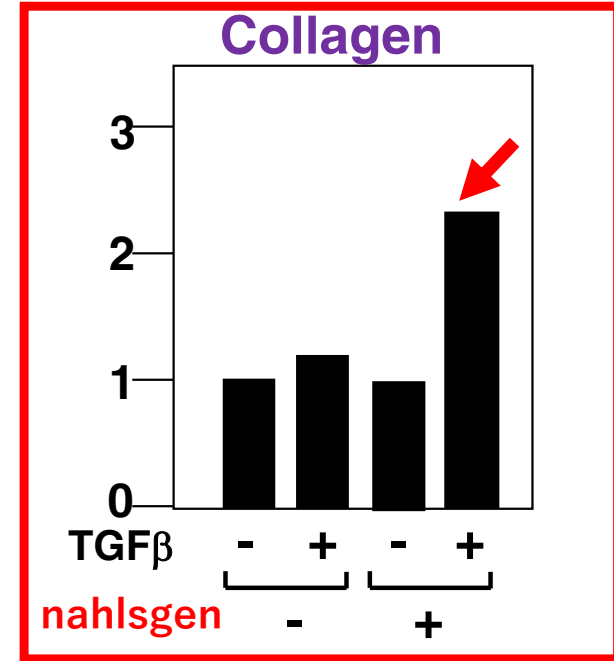
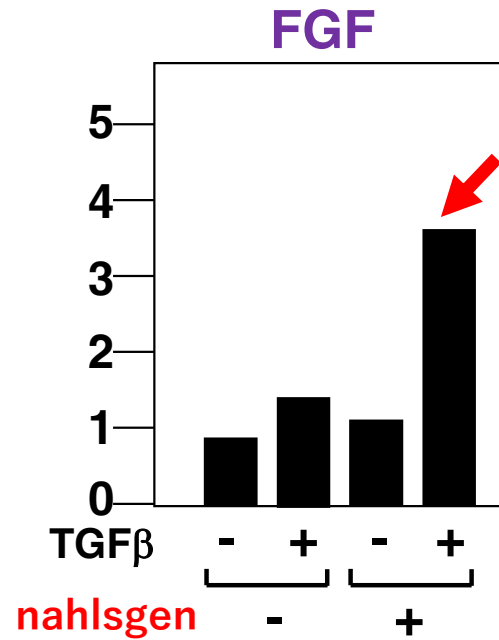
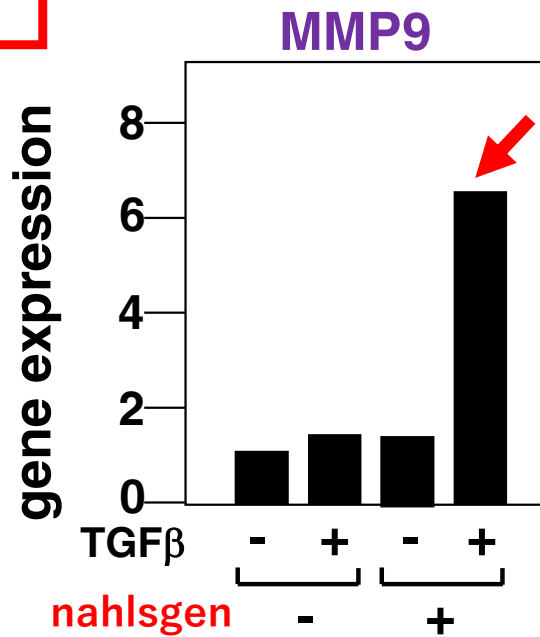
# Wound healing promotion factors



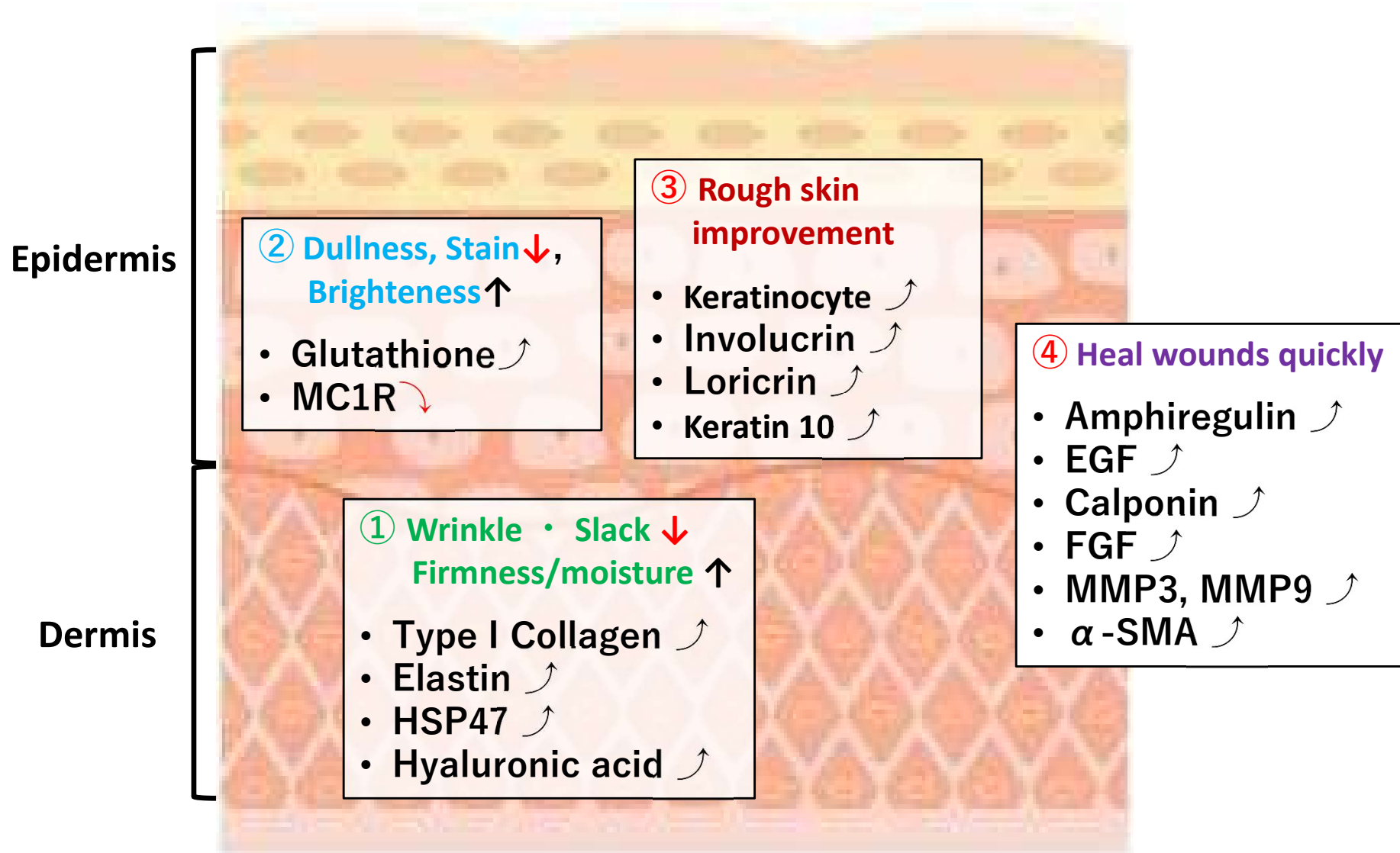
**Nahlsngen** and TGFβ reinforce RNA expression of the factors synergistically.

# In fibroblasts, Nahlsgen and TGF $\beta$ synergistically promotes expression of genes involved in tissue repair

Recent data



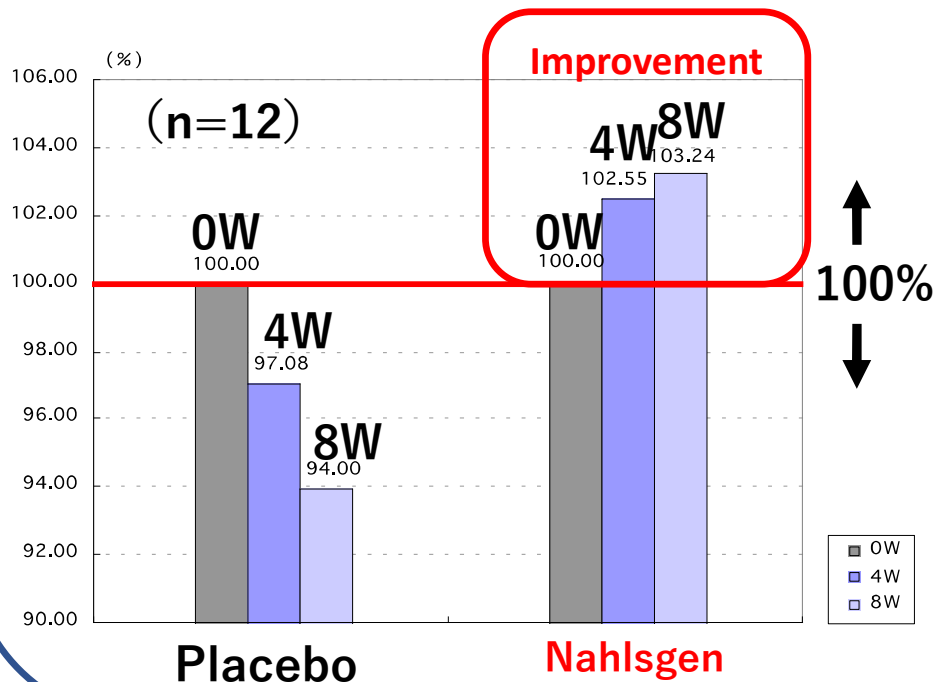
# Summary of Nahlsge's Action



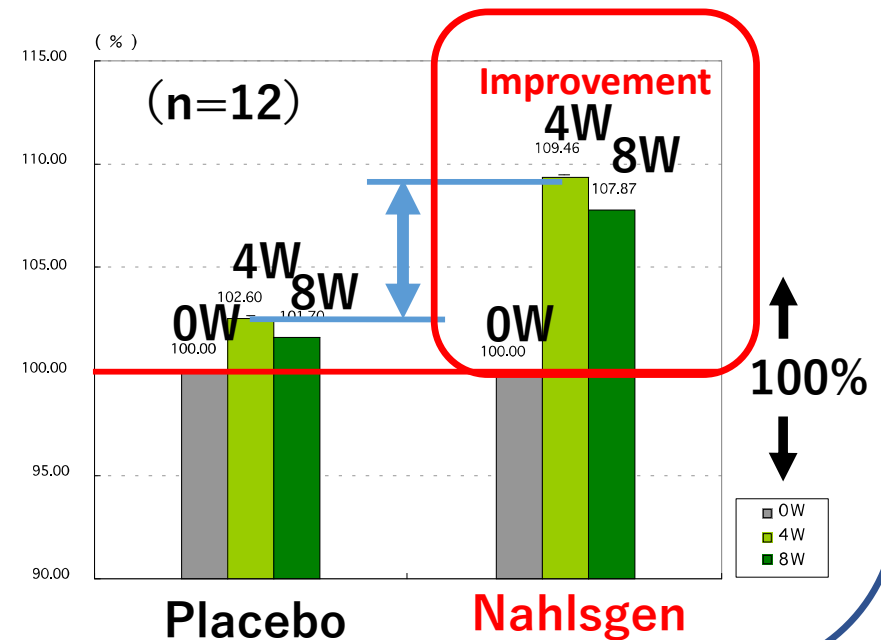
# Nahlsgen Monitor test - 1

General women of their 30s to 50s

## Humidity retention function



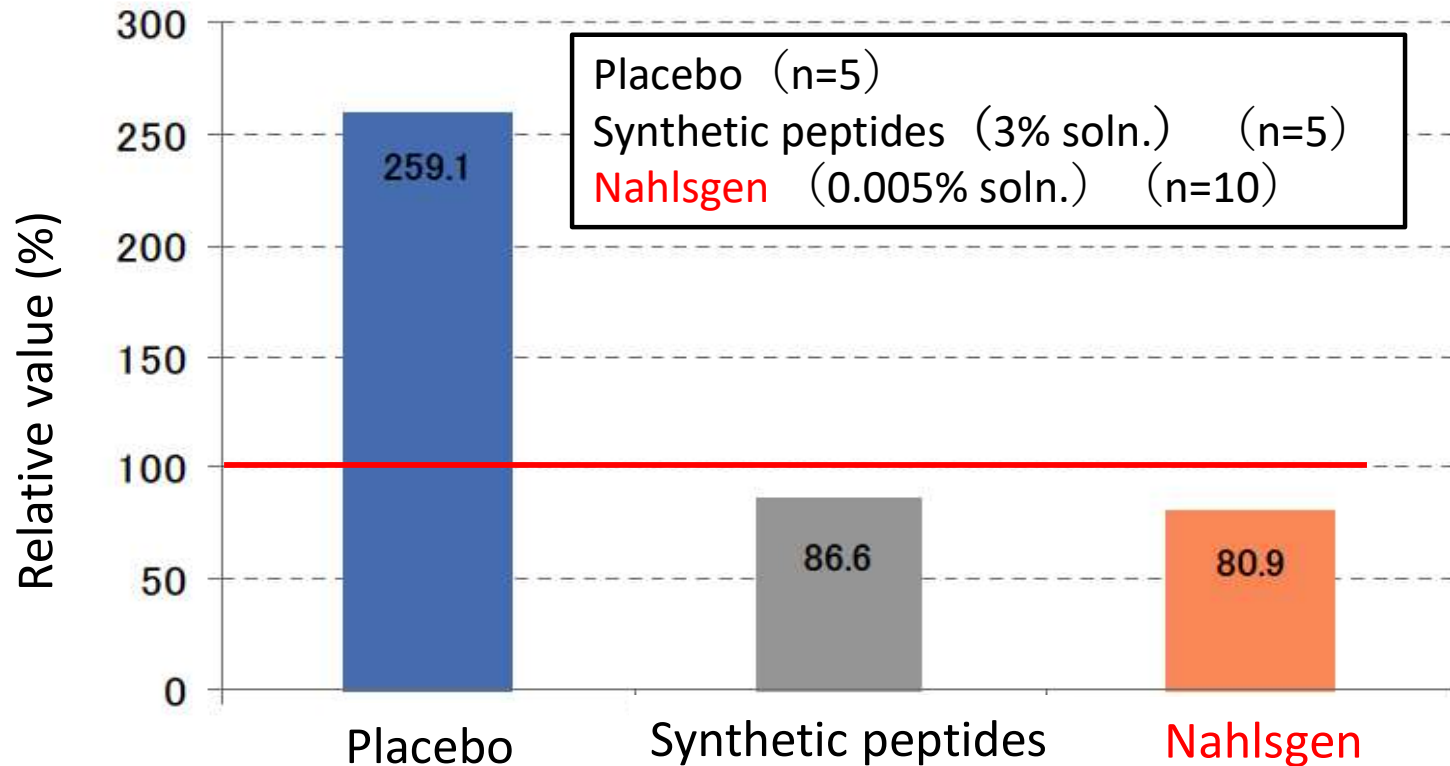
## Elasticity of the skin



**Nahlsgen** enhances a humidity retention and raises elasticity

# Nahlsngen Monitor test - 2

## Wrinkle score after three months continuous use



Face image analysis machine : 「VISIA evolution™」 (Canfield Co., Ltd.)

**Nahlsngen showed wrinkle improvement effect.**

# Cosmetic Ingredient

**Since 2012**



- Nahlsgen 1% BG Solution
- Sold to over 60 cosmetics manufacturers in Japan
- Rodan + Fields in U. S. since 2019

## Cosmetic Ingredient

**RECHARGE** from “Rodan + Fields”

Since 2019



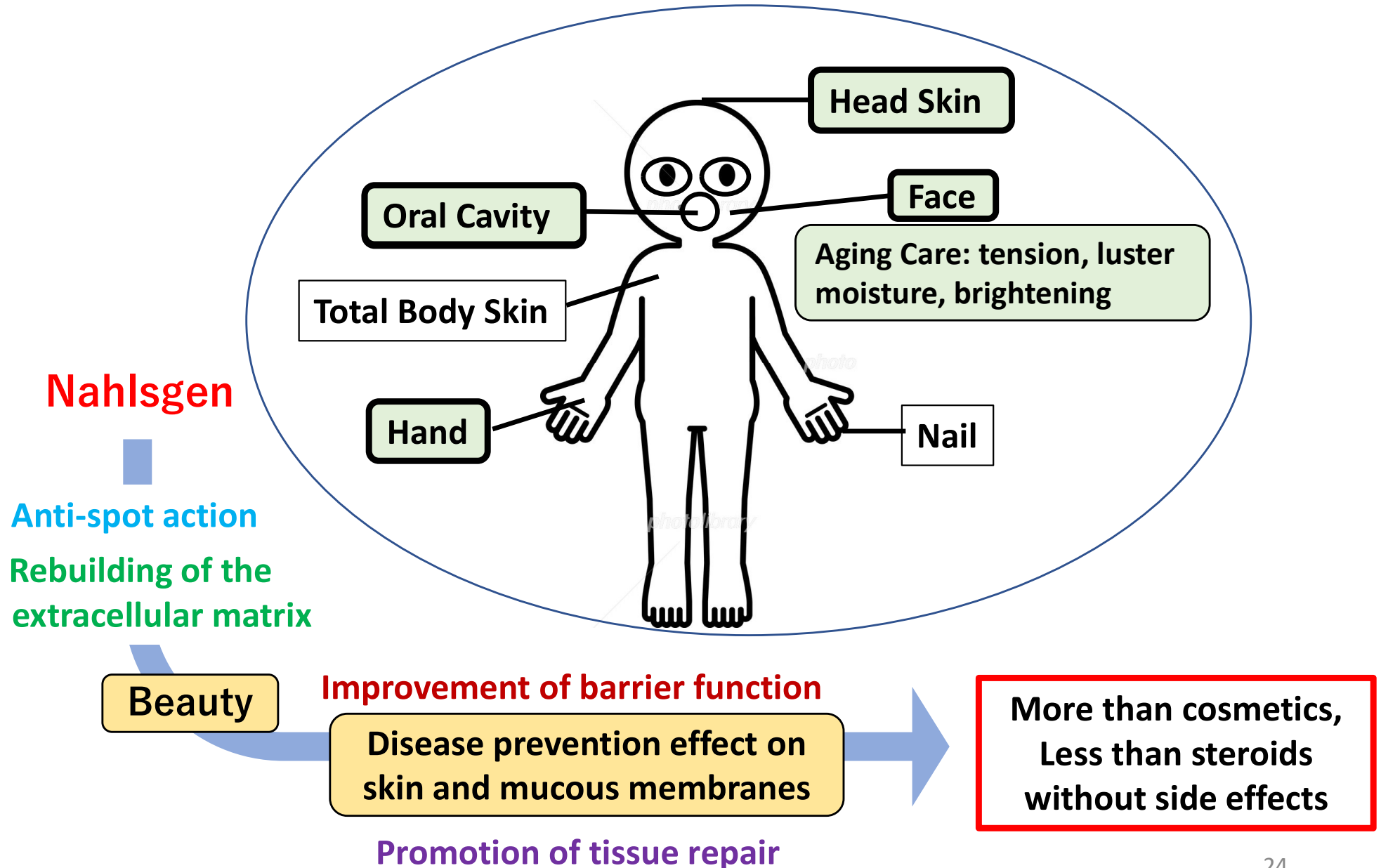
1. Super Cleanser
2. Ultra Boost Moisturizing Treatment (Nahlsigen included)
3. Protect + Blur Broad Spectrum SPF 30 Sunscreen (Nahlsigen included)

## 8. Our products



NAHLS  
CORPORATION

# Our simple cosmetic products based on **Nahlsngen**



## Skin Care Cosmetics



Nahls Mint Plus (Lotion)

**Since 2013**



Nahls Mint Gel

**Since 2015**

Manufacturer : NAHLS CORPORATION  
Supplier : NAHLS CORPORATION

# Hair Growth Stimulant

**Since 2018**



**Nahls Reha (Scalp Lotion)**

**Manufacturer : KAMINOMOTO  
Supplier : TOABO**

## Oral Humectant

**Since 2019**



keora (Oral moisture mist)

keora (Oral moisture gel)

Manufacturer : NAHLS CORPORATION  
Supplier : NISSIN (Co-developer)

## 8. Our products

# Hand Cream

**Since 2022**

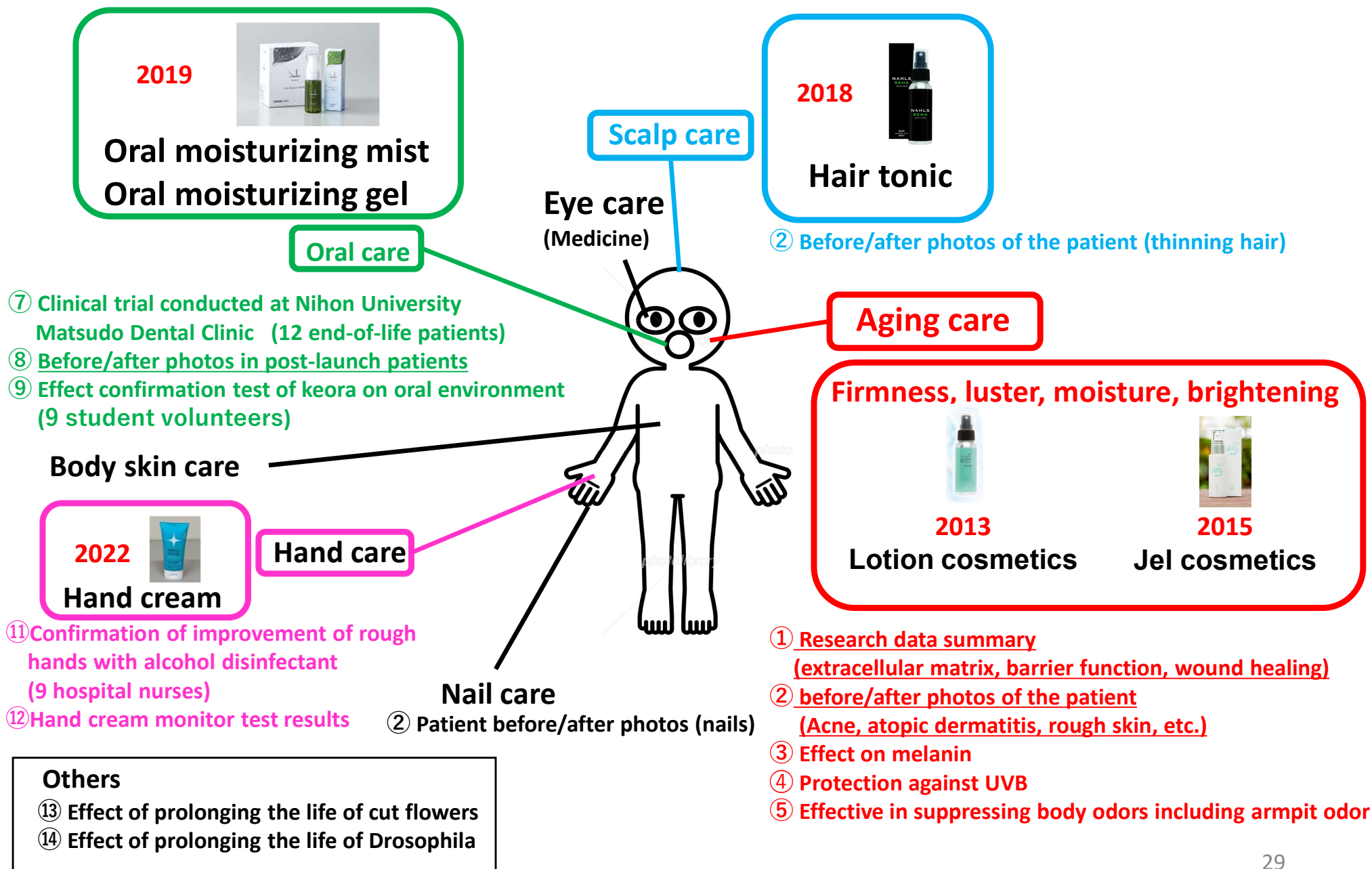


## NAHLS NURSE for Hands

Manufacturer : NAHLS CORPORATION  
Supplier : NAHLS CORPORATION

# 9. Summary of evidence

## Summary of Evidence for Nahlsgen Effectiveness



## 9. Summary of evidence

# Summary of Evidence for Nahlsngen Effectiveness

NO.	Items	Contents/Key word
①	Research data summary (extracellular matrix, glutathione, barrier function, wound healing)	Reconstruction of extracellular matrix: collagen, elastin, HSP, hyaluronic acid Barrier function improvement: keratinocytes, keratin 10, loricrin, involucrin Promote wound healing: FGF, MMPs, $\alpha$ -SMA, Calponin, EGF, Amphiregulin
②	before/after photos of the patient (Acne, atopic dermatitis, rough skin, scalp)	Improvement effect confirmed in patients at aesthetic skin and cosmetic surgery clinics
③	Effects on melanin	③-1 RIKEN: Action to induce "eumelanin < pheomelanin" ③-2 Gifu University: Inhibition of melanosome uptake into keratinocytes
④	Protection against UVB	When human epidermal cells were irradiated with a UVB lamp and measured for cell viability 24 hours later, suppression of the decrease in viability was observed in a Nahlsngen concentration-dependent manner.
⑤	Effectiveness in suppressing body odors including armpit odor	Suppression of generation of armpit odor molecules (German researcher's paper) Deodorant (deodorant) effect on 20 types of odor components that make up body odor
⑦	Clinical trial results conducted at Nihon University Matsudo Dental Clinic (12 end-of-life patients)	Remarkably improved oral environment by treating elderly patients with deteriorated oral environment (moisturizing, tongue coating, crusts, bad breath)
⑧	Before/after photos in post-launch patients	Confirmation of improvement: Oral troubles such as stomatitis, angular stomatitis, cheilitis, tongue coating
⑨	Effect confirmation test of keora on oral environment (10 student volunteers)	Confirmation of improvement: Humidity, tongue coating, bacteria count
⑪	Confirmation of improvement of rough hands with alcohol disinfectant	Confirmed the effect of improving rough hands with Nahlsngen-containing alcohol disinfectant (9 hospital nurses)
⑫	Hand cream monitor test results	Confirmed the effect of improving rough hands with Nahlsngen-containing hand cream
⑬	Effect of prolonging the life of cut flowers	Nahlsngen-enriched water extends the life of cut carnation flowers
⑭	Effect of prolonging the life of Drosophila	Lifespan extension effect confirmed in Drosophila drinking Nahlsngen-enriched water Anti-aging in muscle and gastrointestinal tissue

## List of patents

No	Applicatio n Year	Title	Inventors	Applicants	Patent No (Status)
1	2006	PHOSPHONIC ACID DIESTER DERIVATIVE AND METHOD FOR PRODUCING THEREOF	HIRATAKE JUN, SAKATA KANZO, HAN LIYOU	KYOTO UNIVERSITY	JP5082102 (B2) US2009163725 (A1)(US8129557(B2)) CN101336246 (B)(ZL200680052428.4)
2	2010	COLLAGEN PRODUCTION PROMOTER, PHOTOAGING INHIBITOR, MOISTURIZING FUNCTION IMPROVER, AND SKIN CARE COMPOSITION	YUASA ISAO, KOJIMA AKIKO, HIRATAKE JUN, HAN LIYOU	OSAKA CITY UNIVERSITY KYOTO UNIVERSITY	JP2010270115 (A) JP5686365 (B2)
3	2010	PROTEIN PRODUCTION PROMOTER OF SKIN FIBROBLAST AND PROMOTER FOR MIGRATION AND PROLIFERATION OF KERATINOCYTE	HIRATAKE JUN, WATANABE BUNTA, YUASA ISAO, YUASA AKIKO	KYOTO UNIVERSITY OSAKA CITY UNIVERSITY	JP20100206830 JP2012062266 (A) JP5787246 (B2) (Registered on August 7, 2015)
4	2010	METHOD FOR PRODUCING PHOSPHONIC ACID DIESTER DERIVATIVE	WATANABE BUNTA, HIRATAKE JUN	KYOTO UNIVERSITY	JP2010266317 JP2012116776 (A) (Decision of Refusal dated April 28,2015)
5	2014	ORAL PREVENTIVE OR THERAPEUTIC AGENT FOR ORAL MUCOSAL DISEASE	TERADA HIROSHI, HIROTA KEIJI, TAGO AKIO, YOSHIOKA RYUZO	NAHLS CORPORATION CO., LTD.	JP2014132645 JP2016011262 (A) JP6294773 (B2) (Registered on February 23, 2018)
6	2015	PLANT FRESHNESS RETAINING AGENT COMPOSITION, PLANT GROWTH ACCELERATING AGENT COMPOSITION, PLANT, AND PLANT PRODUCTION METHOD AND PLANT TREATMENT METHOD	YOSHIOKA RYUZO, ISHIDA HIDEAKI	NAHLS CORPORATION CO., LTD. TOABO CORPORATION	JP2015027051 JP2016147841 (A) JP 6457292 (B2) (Registered on December 28, 2018)
7	2015	PREVENTIVE OR THERAPEUTIC AGENT FOR INFLAMMATORY SKIN DISEASE	YOSHIDA HISAHIRO, YOSHIOKA RYUZO, ISHIDA HIDEAKI	NAHLS CORPORATION CO., LTD. TOABO CORPORATION RIKEN	JP2015032533 JP2016155762 (A) JP6550656 (B2) (Registered on July 12, 2019)
8	2015	FILAGGRIN GENE EXPRESSION-PROMOTING AGENT	TANI FUMITO, YOSHIOKA RYUZO, ISHIDA HIDEAKI	NAHLS CORPORATION CO., LTD. TOABO CORPORATION KYOTO UNIVERSITY	JP2015-234880 JP2017100987 (A) JP6778361(B2) (Registered on October 14, 2020)
9	2015	GLUTATHIONE PRODUCTION PROMOTER	HIRATAKE JUN, WATANABE BUNTA, YOSHIOKA RYUZO, ISHIDA HIDEAKI	NAHLS CORPORATION CO., LTD. TOABO CORPORATION KYOTO UNIVERSITY	JP2015235117 JP2017100993 (A) JP6778362(B2) (Registered on October 14, 2020)

## List of patents

10	2016	OPTICAL RESOLUTION METHOD FOR NAHLSGEN	HIRATAKE JUN, WATANABE BUNTA, YOSHIOKA RYUZO, ISHIDA HIDEAKI	NAHLS CORPORATION CO., LTD. KYOTO UNIVERSITY	JP2016179297 JP2018043944(A) JP6826333(B2) (Registered on January 19, 2021) WO2018051972 (A1) CN109715636 (A) EP3514160 (A1) US2019225634 (A1) US10,774,098B2 (Registered on September 15, 2020)
11	2017	OPTICALLY-ACTIVE 2-AMINO-PHOSPHONOALKANE ACID, OPTICALLY-ACTIVE 2-AMINO-PHOSPHONOALKANE ACID SALT, AND HYDRATES OF THESE	WATANABE BUNTA, YOSHIOKA RYUZO, ISHIDA HIDEAKI	NAHLS CORPORATION CO., LTD. KYOTO UNIVERSITY	JP2017081237 (Deemed to be withdraw) WO2018193999 (A1) CN201880025285.0 CN110520432(A) EP18788320.2 EP3613750(A1) US16/605,645 US2020/131207(A1) US11,220,521B2 (Registered on January 11, 2022) JP2019513616 (Examination requested on February 5, 2021)
12	2017	WOUND HEALING PROMOTER	YOSHIOKA RYUZO TANAKA YOKO, YAGUCHI MANABU, TANAKA TAKASHI	NAHLS CORPORATION CO., LTD. NIHON UNIVERSITY RIKEN	JP2017081239 (Deemed to be withdraw) WO2018194000(A1) CN201880025450.2 CN110536688(A) EP18788419.2 EP3613422(A1)(Withdrawn) US16/605,625 US2020/121700(A1) US11,090,318B2(Registered on August 17, 2021) JP2019513617 (Examination requested on March 11, 2021)
13	2017	INVOLUCRIN GENE EXPRESSION PROMOTER	TANI FUMITO, YOSHIOKA RYUZO, ISHIDA HIDEAKI	NAHLS CORPORATION CO., LTD. TOABO CORPORATION KYOTO UNIVERSITY	JP2017112353 JP2018203682 (A) (abandoned due to Examination has not been requested)
14	2018	DEODORANT	MATUHI KENJI, YOSHIOKA RYUZO, ISHIDA HIDEAKI	NAHLS CORPORATION CO., LTD. TOABO CORPORATION	JP2018163456 JP2020033326 (A) (Examination requested on July 16, 2021)

## Papers

No.	Title	Journals	Authors
1	Design, Synthesis, and Evaluation of $\gamma$ -Phosphono Diester Analogues of Glutamate as Highly Potent Inhibitors and Active Site Probes of $\gamma$ -Glutamyl Transpeptidase	Biochemistry, 46, 1432-1447, (2007)	Liyou Han, Jun Hiratake, Akane Kamiyama, and Kanzo Sakata
2	$\gamma$ -Glutamyl transpeptidase (GGT)の新規阻害剤 – GGTの生理的意義をさぐる新たな化学ツール	和光純薬時報, 76(3), 2-6, (2008)	平竹潤
3	Preventive effect of GGsTop, a novel and selective $\gamma$ -glutamyl Transpeptidase inhibitor, on ischemia/reperfusion-induced renal injury in rats.	J Pharmacol Exp Ther, 339(3), 945-951, (2011).	Yamamoto S, Watanabe B, Hiratake J, Tanaka R, Ohkita M, Matsumura Y.
4	Inhibiting Glutathione Metabolism in Lung Lining Fluid as a Strategy to Augment Antioxidant Defense.	Curr Enzym Inhib., Jul;7(2), 71-78, (2011)	Joyce-Brady M, Hiratake J.
5	$\gamma$ -グルタミルトランスぺプチダーゼ(GGT)阻害剤によるコラーゲンおよびエラスチン産生能の亢進効果とそのメカニズム	日本化粧品学会誌, vol.36, No.2, 93-100, (2012).	湯浅(小島)明子、林綾子、韓立友、渡辺文太、平竹潤、湯浅勲
6	$\gamma$ -glutamyltranspeptidase and its precursor	Handbook of Proteolytic Enzymes, 3 <sup>rd</sup> Ed., Dec. 2012	Hiratake J., Suzuki H., Fukuyama K., Wada K., Kumagai H.
7	Phosphonate-based irreversible inhibitors of human $\gamma$ -glutamyl transpeptidase (GGT). GGsTop is a non-toxic and highly selective inhibitor with critical electrostatic interaction with an active-site residue Lys562 for enhanced inhibitory activity	Bioorganic & Medicinal Chemistry, 24, 5340-5352, (2016)	Akane Kamiyama,-Mado Nakajima, Liyou Han, Kei Wada, Masaharu Mizutani Yukiko Tabuchi, Akiko Kojima-Yuasa, Isao Matsui-Yuasa, Hideyuki Suzuki, Keiichi Fukuyama, Bunta Watanabe, Jun Hiratake
8	Synthesis and evaluation of the inhibitory activity of the four stereoisomers of the potent and selective human $\gamma$ -glutamyl transpeptidase inhibitor GGsTop	Bioorganic & Medicinal Chemistry Letters, 27, 4920-4924, (2017)	Bunta Watanabe, Yukiko Tabuchi, Kei Wada, Jun Hiratake
9	An improved synthesis of the potent and selective $\gamma$ -glutamyl transpeptidase inhibitor GGsTop together with an inhibitory activity evaluation of its potential hydrolysis products	Tetrahedron Letters, 58, 3700-3703, (2017)	Bunta Watanabe, Tatsuya Morikita, Yukiko Tabuchi, Ryoto Kobayashi, Chunjie Li, Masakazu Yamamoto, Takao Koeduka, Jun Hiratake