CosmeRNA

Novel AGA Solution with RNA technology

BIONEER Innovation • Value • Discovery

siRNAgen THERAPEUTICS

Bioneer Corp.

Androgenetic Alopecia

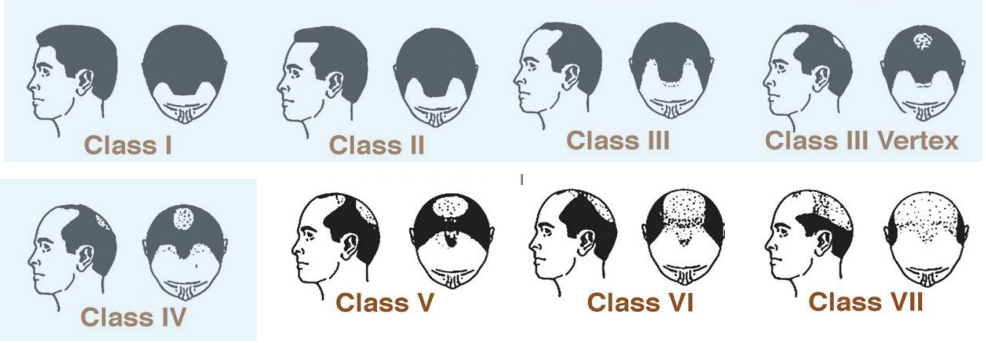
Androgen & androgen receptor action

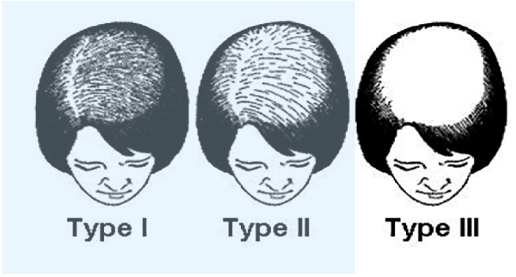
COSME:RNA

Androgenetic Alopecia

Androgenetic Alopecia (AGA)? A hormonally-driven condition

Leads to
Progressive Hair Loss





Affects
(Europe)

Prevalence of AGA by age group

80%

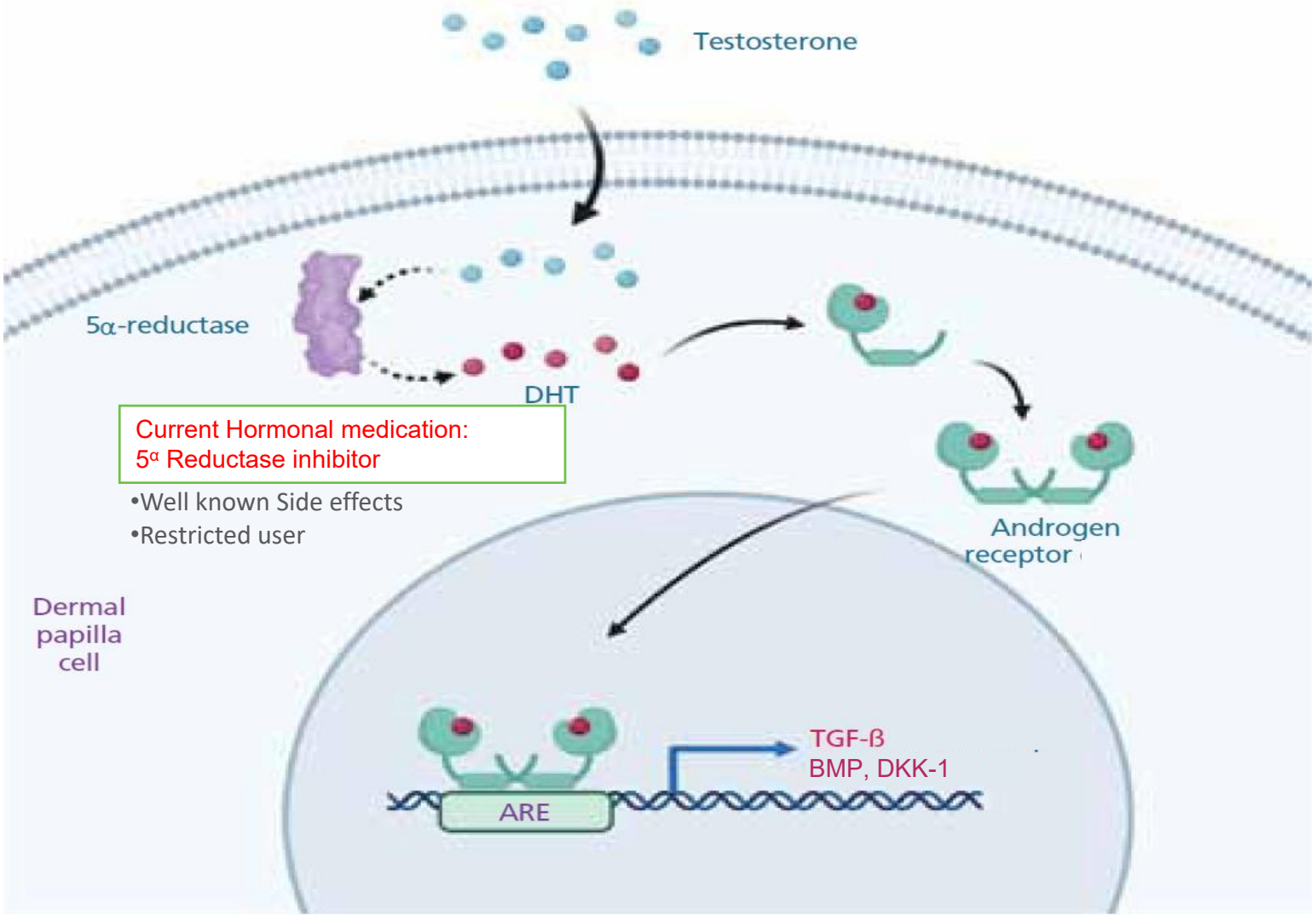
	30~39	40~49	50~59
Age Grade	n (%) (n=97)	n (%) (n=57)	n (%) (n=60)
Type 1 ~ Type 4a	47	27	26
	48%	**47%**	**43%**

50%

	30~39	40~49	50~59
Age Grade	n (%)	n (%)	n (%)
	(n=113)	(n=89)	(n=65)
Grade 1~2	23	26	28
	20%	**29%**	**43%**

1. Androgenetic Alopecia, https://pubmed.ncbi.nlm.nih.gov/28613674/
2. AHLA, https://www.americanhairloss.org/men_hair_loss/index.html
3. Alopecia Market Forecast to 2030, Reports And Data, 2022
4. Frequency, severity and related factors of androgenetic alopecia in dermatology outpatient clinic, An Bras Dermatol. 2017 Jan-Feb; 92(1): 35–40.

Androgen & Androgen Receptor in AGA



Androgenetic Alopecia (AGA)?

A hormonally-driven condition to leads to progressive hair loss.

Testosterone is converted into **DHT** by **5-α reductase**, combined with **Androgen Receptor(AR)**

Only treatments with severe side effects on QoL(Quality of Life) exist in the current market

1. Julieta María Ceruti, Androgens and androgen receptor action in skin and hair follicle, Molecular and Cellular Endocriology, Volume 465, 15 April 2018, Pages 122-133 https://www.sciencedirect.com/science/article/abs/pii/S0303720717304926?via%3Dihub
2. Androgenetic Alopecia, https://www.ncbi.nlm.nih.gov/books/NBK430924/

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Use of siRNA as antiaging cosmeceuticals

J. Cosmet. Sci., 64, 1–14 (November/December 2013)

Use of small RNA as antiaging cosmeceuticals

Pingjing Zhang [1], Jianxin Chen [1], Tiejun Li [1], York Yuanyuan Zhu [1]

Affiliation

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Abstract

Over the past two decades, RNA interference (RNAi) has achieved great improvements in medicine, which has benefited the development of innovative cosmeceutical products, particular, to antiaging cosmeceuticals. A variety of ongoing research has tried to employ small RNAs-small interference RNA and microRNA as new cosmeceutical ingredients. Furthermore, several skin care companies have released new small RNA products in cosmetic market. In this review, we will describe the latest and most advanced approaches and strategies of using small RNA as antiaging cosmetics, including investigations on aging-related genes that small RNA target, method of delivering them, and challenges in the development of RNAi-based therapeutics for skin care cosmeceuticals. It is certain that advancement in this direction will evolve a new landscape for innovative antiaging cosmeceuticals.

According to the review article on analysis of the recent research trend for innovations of cosmeceuticals,

- Researches on cosmeceuticals utilizing novel small RNA (siRNA, microRNA) technology are very active and were stated as a crucial business strategy
- **The best way to confirm the efficacy of siRNA on AGA is to degrade mRNA of AR to suppress protein expression, and topical application is suggested for a better performance.**

Table I.
Small RNA in Antiaging Cosmeceuticals

Type of small RNA	Gene target	Application	References
miRNA	Tyrosinase	Whitening	23,24
siRNA	MITF	Whitening	25,26
siRNA	P53	Whitening	7
miRNA inhibitor	miR-29	Antiwrinkle	27,28
miRNA	Hyaluronidase	Moisturizing	19
siRNA	Androgen receptors	Hair care	29,30
siRNA	Tbx21	Hair care	31
miRNA inhibitor	miR-31	Hair care	32
miRNA	LSD1/2, DNMT1, MECP1/2	Antiaging	33

1. J Cosmet Sci. 2013 Nov-Dec;64(6):455-68.

Current limitations to develop as cosmetics

RNA is difficult to get across the Skin and causes immune stimulation

Our unique proprietary chemistry enable delivery across skin with no safety issues

RNAi typically needs complex chemistry and formulation, making it expensive to make

Our proprietary manufacturing IP and know-how enable large scale manufacturing at a scalable cost

RNA rapidly degrades normally and the short shelf-life makes it difficult to supply OTC

Our shelf life is over 1 year in room temperature conditions, making OTC possible

SAMiRNA is a breakthrough platform for topical RNAi

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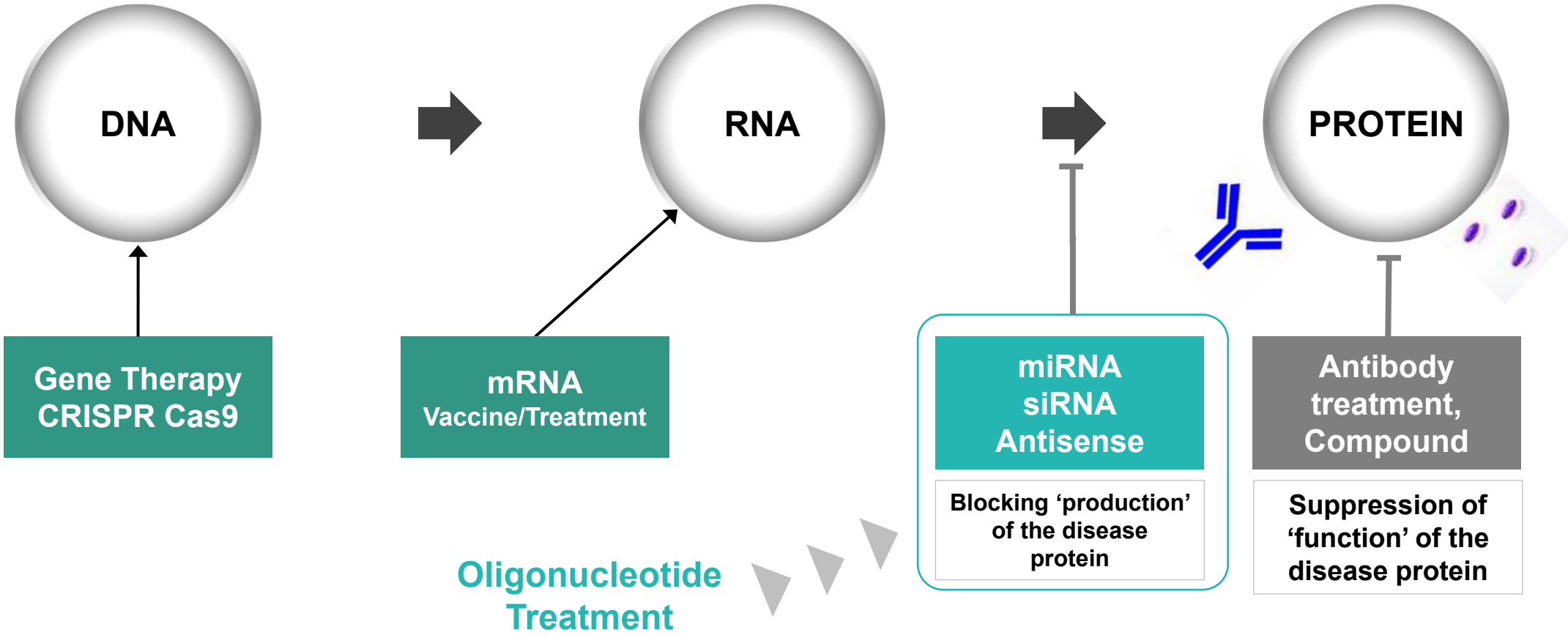
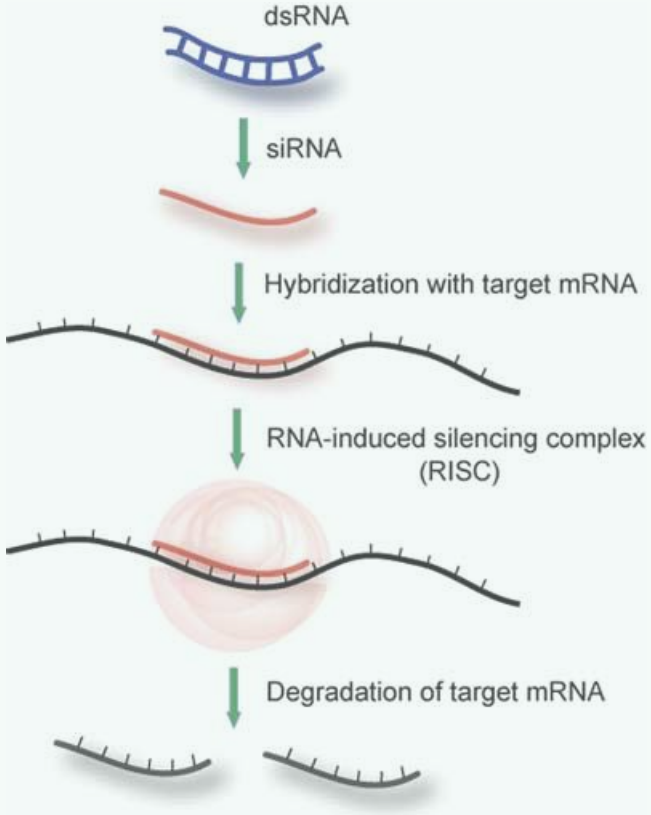
si-RNA : novel technology targeting mRNA

- Central Dogma : From DNA to Protein

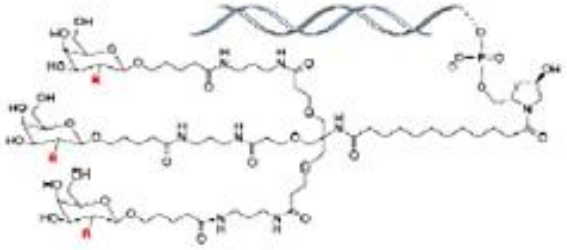


si-RNA : novel technology targeting mRNA



siRNA only functions when its antisense strand is completely base-paired to the target mRNA.

Naked (Conjugated) RNAi



Alnylam · arrowhead pharmaceuticals · Dicerna pharmaceuticals · SILENCE THERAPEUTICS

Poor bioavailability & PK, delivery limited to liver

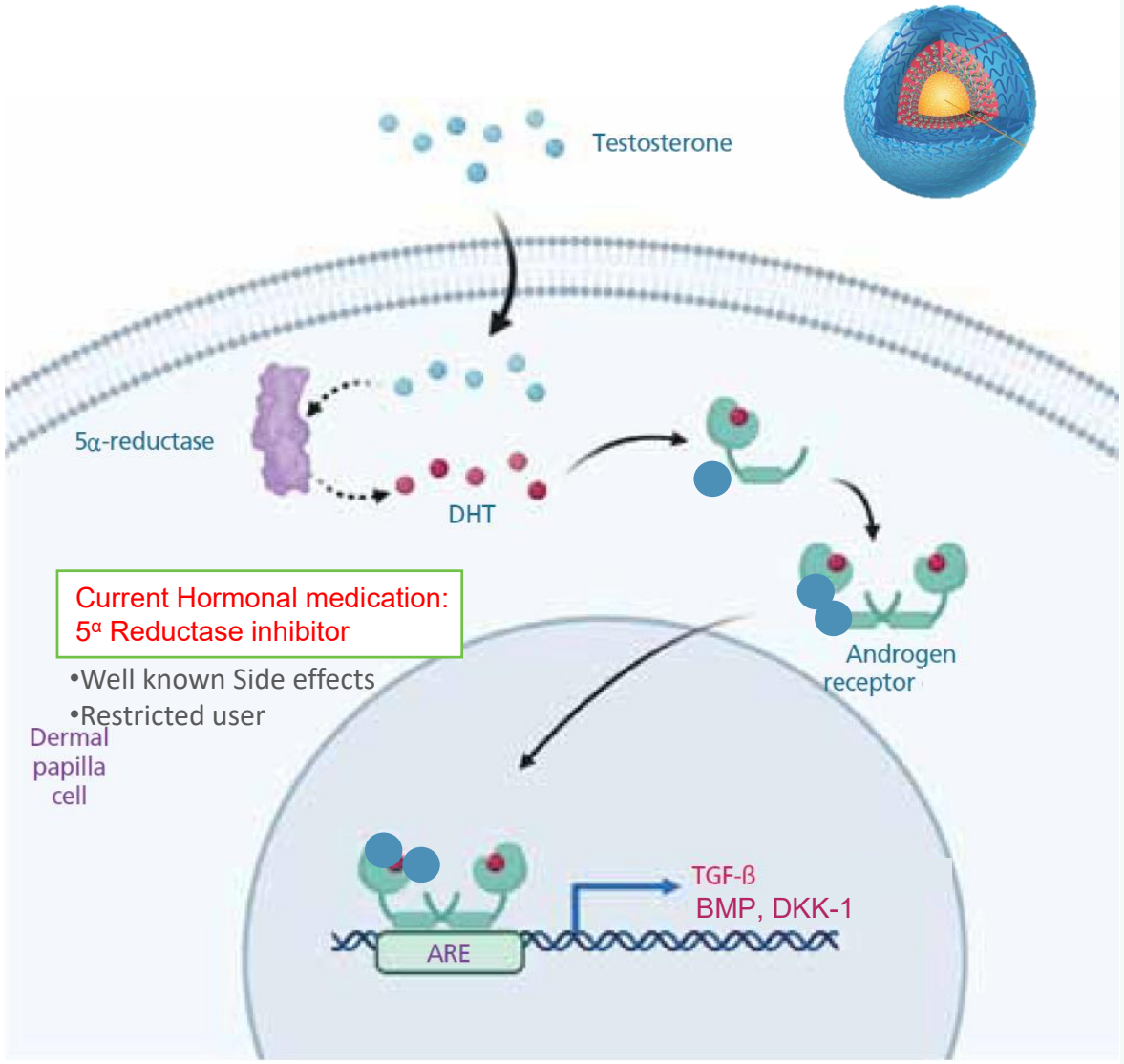
Nanoparticle Encapsulation

Alnylam · ARUNABIO · ReCode THERAPEUTICS

Toxicity, difficulty manufacturing & scaling, unstable

Limitation of RNAi therapeutics

SAMiRNA-AR68 with AR Silencing technology



SAMiRNA-AR68:
Nanoparticle-type si-RNA Targeting AR mRNA

INCI Name:
Stearyldisulfidehexyl DNA-2-PEG-45/SH-RNA-1

Technology:
Self-Assembled-Micelle Inhibitory RNA

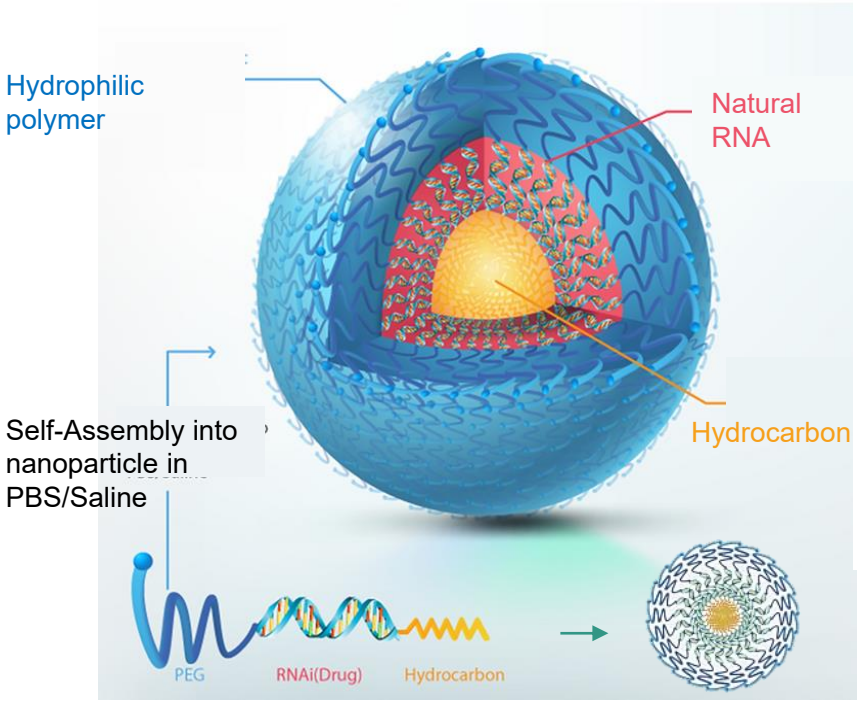
Morphology:
Nanoparticle-type si-RNA targeting AR mRNA in Dermal papilla cell

MoA:
Suppressing AR mRNA and protein level in HFDPc to cause AGA

Function:
Ameliorates the symptoms of AGA

AR mRNA targeting SAMi RNA - AR68 ameliorates AGA

a. Schematic of SAMiRNA nanoparticles



A Self-Assembled micelle-forming nanoparticle, based on the double-conjugated module

Review > Arch Pharm Res. 2018 Sep;41(9):867-874. doi: 10.1007/s12272-018-1069-4.
Epub 2018 Aug 22.

The cutting-edge technologies of siRNA delivery and their application in clinical trials

Kyuri Lee [1], Bora Jang [1], You-Ri Lee [1], Eun-Young Suh [1], Ji-Seon Yoo [1], Mi-Jin Lee [1], Joo-Young Lee [1], Hyukjin Lee [2]

Affiliations + expand

PMID: 30136248 DOI: 10.1007/s12272-018-1069-4

Abstract

siRNA therapeutics allows precise regulation of disease specific gene expression to treat various diseases. Although gene silencing approaches using siRNA therapeutics shows some promising results in the treatment of gene-related diseases, the practical applications has been limited by problems such as inefficient in vivo delivery to target cells and nonspecific immune responses after systemic or local administration. To overcome these issues, various in vivo delivery platforms have been introduced. Here we provide an overview for three different platform technologies for the in vivo delivery of therapeutic siRNAs (siRNA-GalNAc conjugate, SAMiRNA technology, and LNP-based delivery method) and their applications in the treatment of various diseases. In addition, a brief introduction to some rare diseases and mechanisms of siRNA therapeutics-mediated treatment is described.

scientific reports

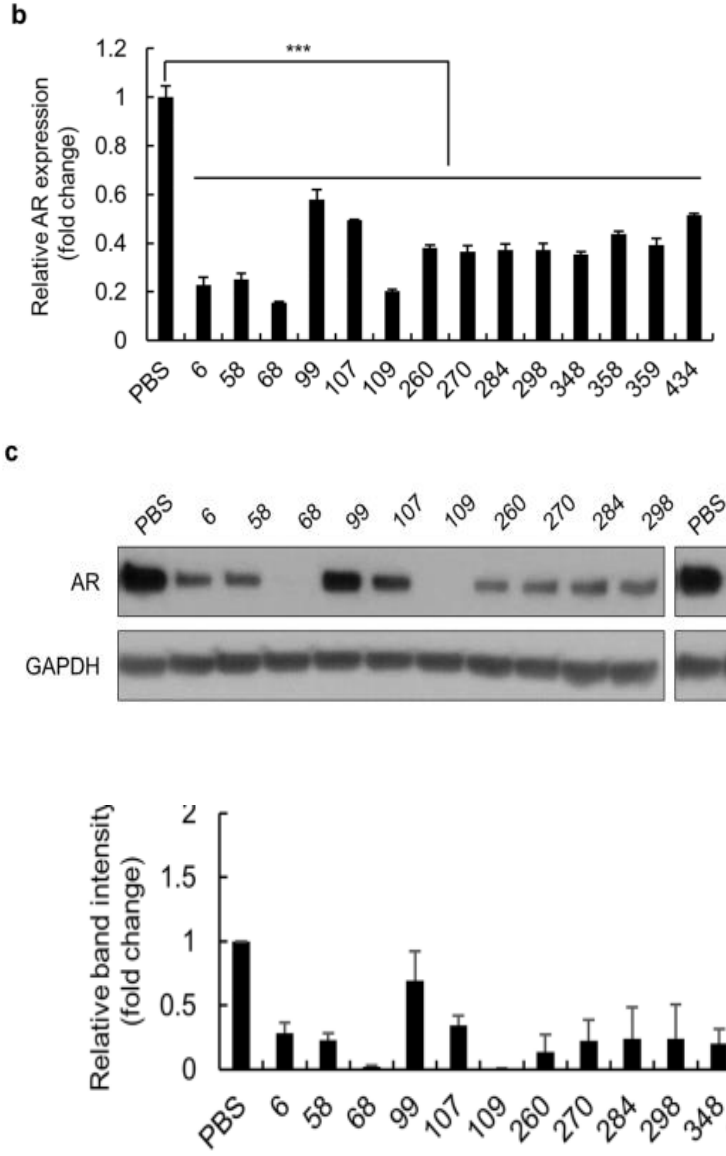
Weekly treatment with SAMiRNA targeting the androgen receptor ameliorates androgenetic alopecia

Sung-Il Yun[1,5], Sang-Kyu Lee[2,5], Eun-Ah Goh[2], Oh Seung Kwon[2], Woorim Choi[2], Jangseon Kim[2], Mi Sun Lee[2], Soon Ja Choi[2], Seung Sik Lim[1], Tae Kee Moon[3], Sin Hae Kim[3], Keeyeol Kyong[4], Gaewon Nam[4] & Han-Oh Park[1,2]

Androgenetic alopecia (AGA) is the most common type of hair loss in men and women. Dihydrotestosterone (DHT) and androgen receptor (AR) levels are increased in patients with AGA, and DHT-AR signaling correlates strongly with AGA pathogenesis. In this study, treatment with self-assembled micelle inhibitory RNA (SAMiRNA) nanoparticle-type siRNA selectively suppressed AR expression in vitro. Clinical studies with application of SAMiRNA to the scalp and massaging to deliver it to the hair follicle confirmed its efficacy in AGA. For identification of a potent SAMiRNA for AR silencing, 547 SAMiRNA candidates were synthesized and screened. SAMiRNA-AR68 (AR68) was the most potent and could be efficiently delivered to human follicle dermal papilla cells (HFDPCs) and hair follicles, and this treatment decreased the AR mRNA and protein levels. We confirmed that 10 μM AR68 elicits no innate immune response in human PBMCs and no cytotoxicity up to 20 μM with HFDP and HaCaT cells. Clinical studies were performed in a randomized and double-blind manner with two different doses and frequencies. In the low-dose (0.5 mg/ml) clinical study, AR68 was applied three times per week for 24 weeks, and through quantitative analysis using a phototrichogram, we confirmed increases in total hair counts. In the 24-week long high-dose (5 mg/ml) clinical study, AR68 showed average additional hair growth of 1.3-1.9 hairs/cm² per month, which is comparable to finasteride. No side effects were observed. Therefore, SAMiRNA targeting AR mRNA is a potential novel topical treatment for AGA.

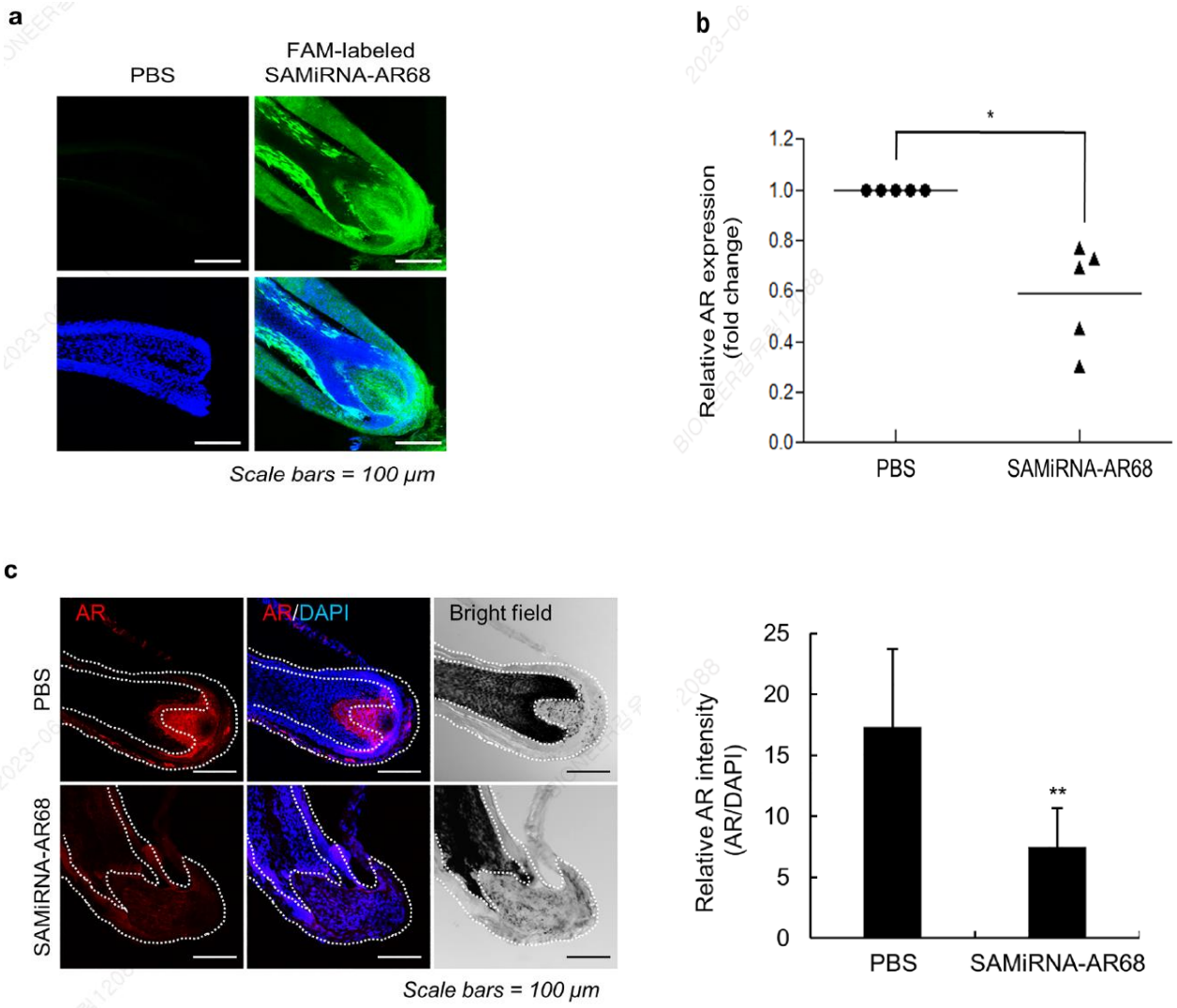
For identification of a potent SAMiRNA for AR silencing, 547 SAMiRNA candidates were synthesized and screened.
SAMiRNA-AR68 (AR68) was the **most potent and could be efficiently delivered to human follicle dermal papilla cells (HFDPCs) and hair follicles, and this treatment decreased the AR mRNA and protein levels.**
-No cytotoxicity up to 20 μM with HFDP and HaCaT cells.
-A randomized and double-blind clinical study with the low does and high dose(0.5mg/ml and 5mg/ml)
-In the 24-week long high-dose (5 mg/ml) clinical study, AR68 showed average additional hair growth of 1.3-1.9 hairs/cm2 per month, which is -comparable to finasteride. No side effects were observed.
Therefore, SAMiRNA targeting AR mRNA is a potential novel topical treatment for AGA

SAMiRNA - AR68 : Screening of potent SAMiRNAs targeting AR in Hair Follicle



(b, c) LNCaP cells treated with PBS or 14 SAMiRNA candidates for 48 h. ***p<0.001(b)Total RNA extracts were subjected to quantitative polymerase chain reaction (qPCR) assays to evaluate AR knockdown efficacy, and AR expression was normalized to the expression of the ribosomal protein lateral stalk subunit P0 (RPLP0) gene (c). Whole-cell lysates were subjected to immunoblot analysis to compare the protein levels of AR and GAPDH. The intensity of the AR and GAPDH bands was quantified by ImageJ software, and AR protein expression was normalized to glyceraldehyde-3-phosphate dehydrogenase (GAPDH) values (c, lower panel).

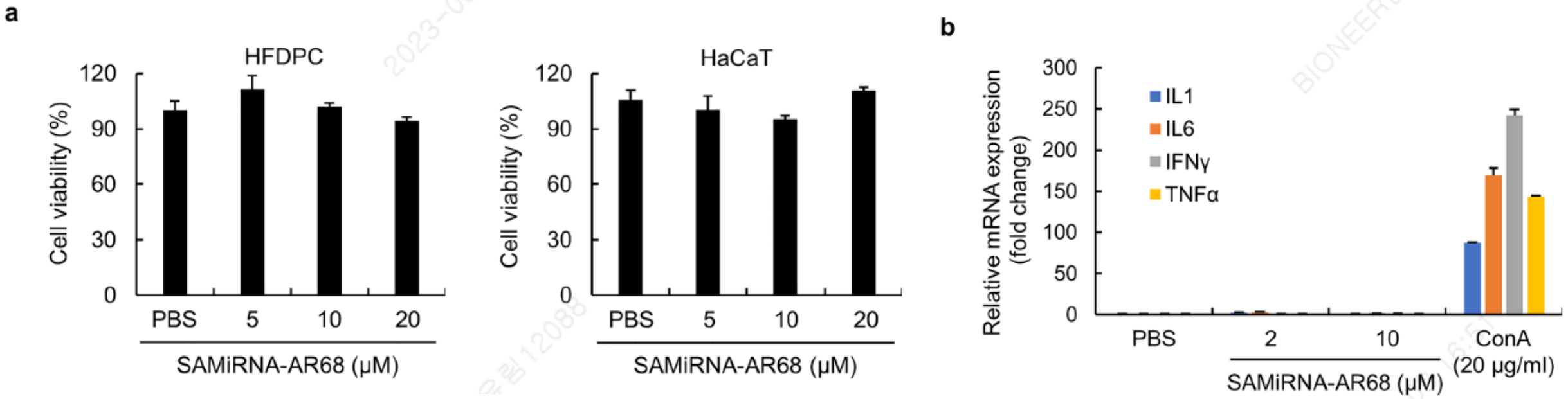
SAMiRNA-AR68: AR Silencing in HF



AR silencing efficacy of SAMiRNA-AR68 in human hair follicles.

(a)Plucked human hair follicles were treated with PBS or 10 μM FAM-labeled SAMiRNA-AR68 in culture medium for 24 h. Hair follicles were subjected to immunofluorescence (IF) analysis and counterstained with 4′,6-diamidino-2-phenylindole (DAPI). Scale bars = 100 μm. (**b**) Plucked human hair follicles were treated with PBS or 10 μM SAMiRNA-AR68 for 48 h. Total RNA extracts from hair bulbs were subjected to qPCR assays, and AR expression was normalized to that of the RPLP0 gene. (**c**) Plucked human hair follicles were treated with PBS or 10 μM SAMiRNA-AR68 for 48 h. IF analysis of the plucked vertex hair follicle section incubated with an anti-AR antibody and counterstained with DAPI. Scale bars = 100 μm. Levels of AR protein were measured by the mean fluorescence intensity using ZEN software. Data are shown as the mean value ± SD (n = 8 hairs/group) normalized for DAPI intensity. Statistical significance was assessed by two-sided Student's t test, $^{*}p < 0.05$ and $^{**}p < 0.01$.

SAMiRNA-AR68: Safety



(**a**) HFDP and HaCaT cells were treated with PBS or the indicated dose of SAMiRNA-AR68 for 72 h. WST-1 assays were performed to measure cell viability. (**b**) Human PBMCs were treated with 20 μg/ml concanavalin A (ConA) as a positive control, PBS, or the indicated doses of SAMiRNA-AR68 for 6 h. Total RNA extracts were subjected to qPCR assays to evaluate the expression of proinflammatory cytokines, including IL-1β, IL-6, INF-γ and TNF-α, normalized to that of the ribosomal protein L13A (RPL13A) gene.

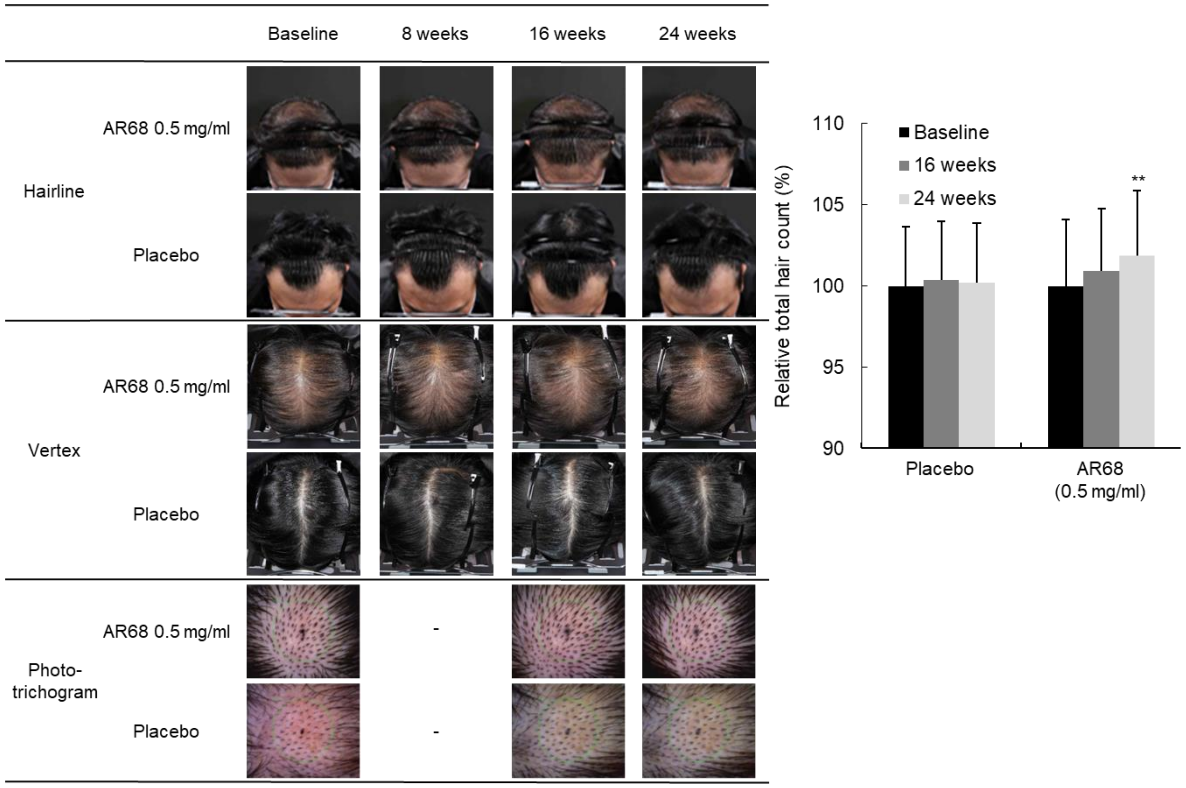
Clinical tests for AGA patients – Efficacy evaluation

- **Proven efficacy by domestic and international clinical tests for AGA patients, which are independently designed for different concentrations and dosage frequencies.**
  - **Double-blind, randomized, placebo-controlled tests**

Low-concentration (0.5 mg/ml) clinical trial	High-concentration(5 mg/ml) clinical trial 1
• Institution : Global derma-clinical test center of Seowon University (45) • Research design : 24 weeks of applying Low-concentrated(0.5 mg/ml) COSMERNA-68, 3 times per week • Method : 1ml of application on the scalp for 3 times per week, with 5 minutes of massaging for better absorption	• Institution : Ellead Skin & Bio Research (43) • Research design : : 24 weeks of applying high-concentrated (5 mg/ml) COSMERNA-68, once per week • Method : 1ml of application on the scalp once per week, with 5 minutes of massaging for better absorption

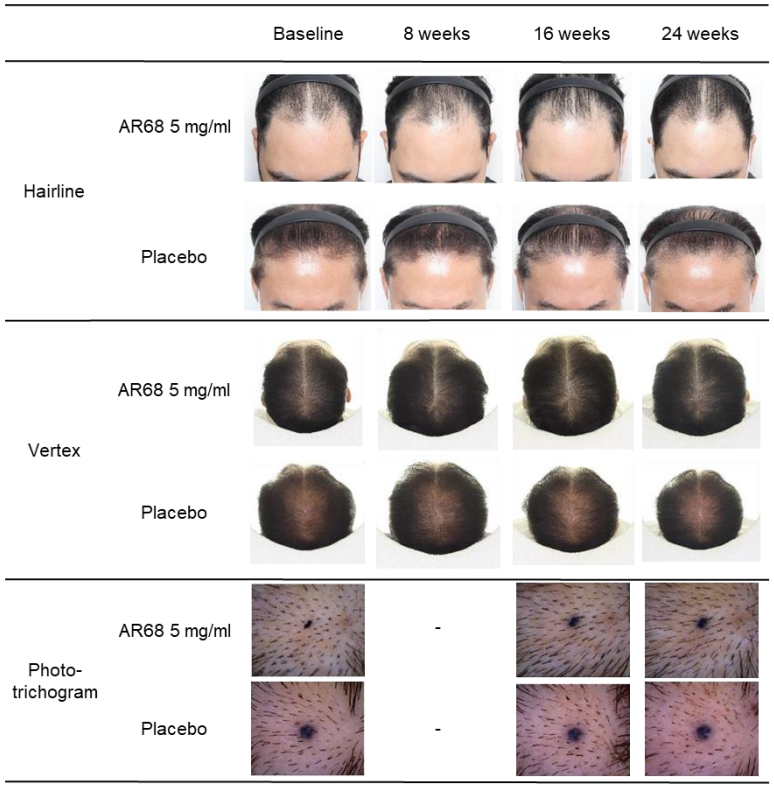
Clinical tests on AGA patients – Efficacy evaluation

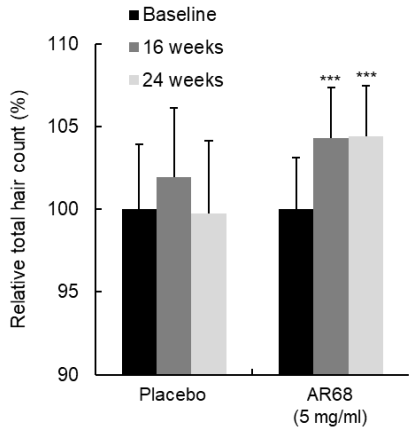
Low-concentration (0.5 mg/ml) clinical trial



Δ Total hair counts (n/cm²)	COSMERNA-68 (n=22)	Placebo (n=23)	*p*-value
	Mean ± SD	Mean ± SD	
16 weeks	0.864 ± 2.189	0.435 ± 2.660	0.477
24 weeks	2.273 ± 3.089	0.304 ± 2.653	0.043*

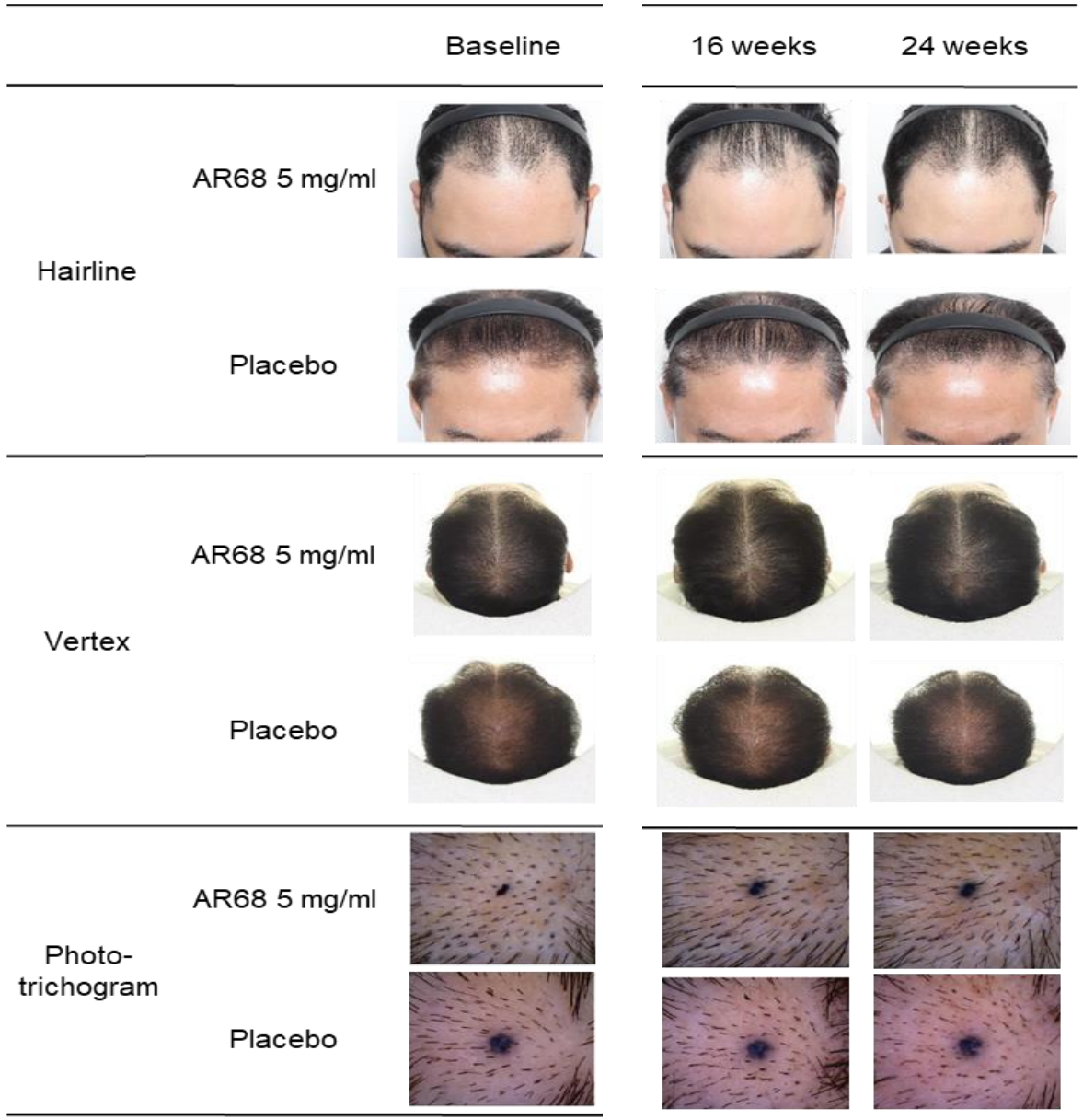
High-concentration (5 mg/ml) clinical trial

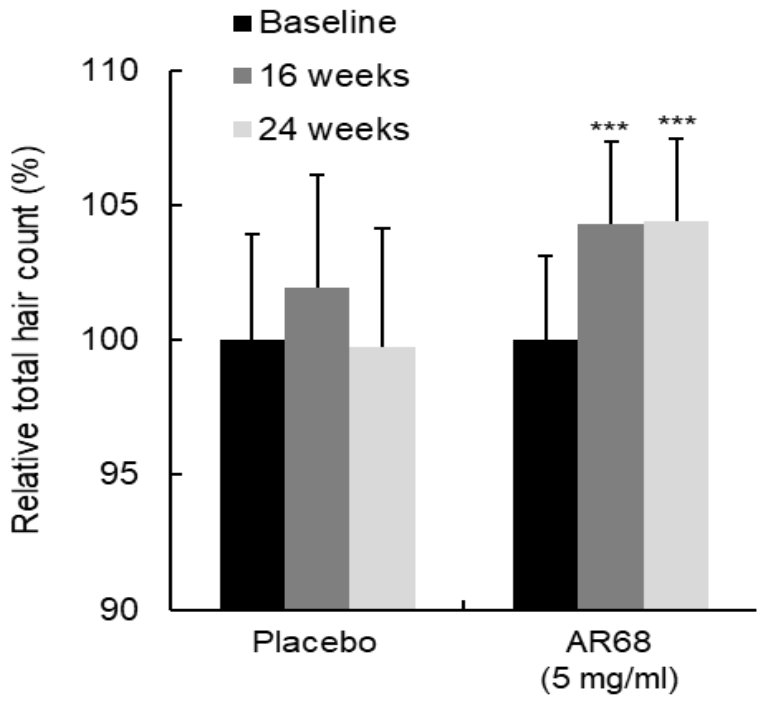




Δ Total hair counts (n/cm²)	COSMERNA-68 (n=22)	Placebo (n=21)	*p*-value
	Mean ± SD	Mean ± SD	
16 weeks	7.545 ± 7.896	3.714 ± 10.335	0.279
24 weeks	7.727 ± 8.659	-0.190 ± 12.875	0.026*

Clinical tests on AGA patients – Efficacy evaluation





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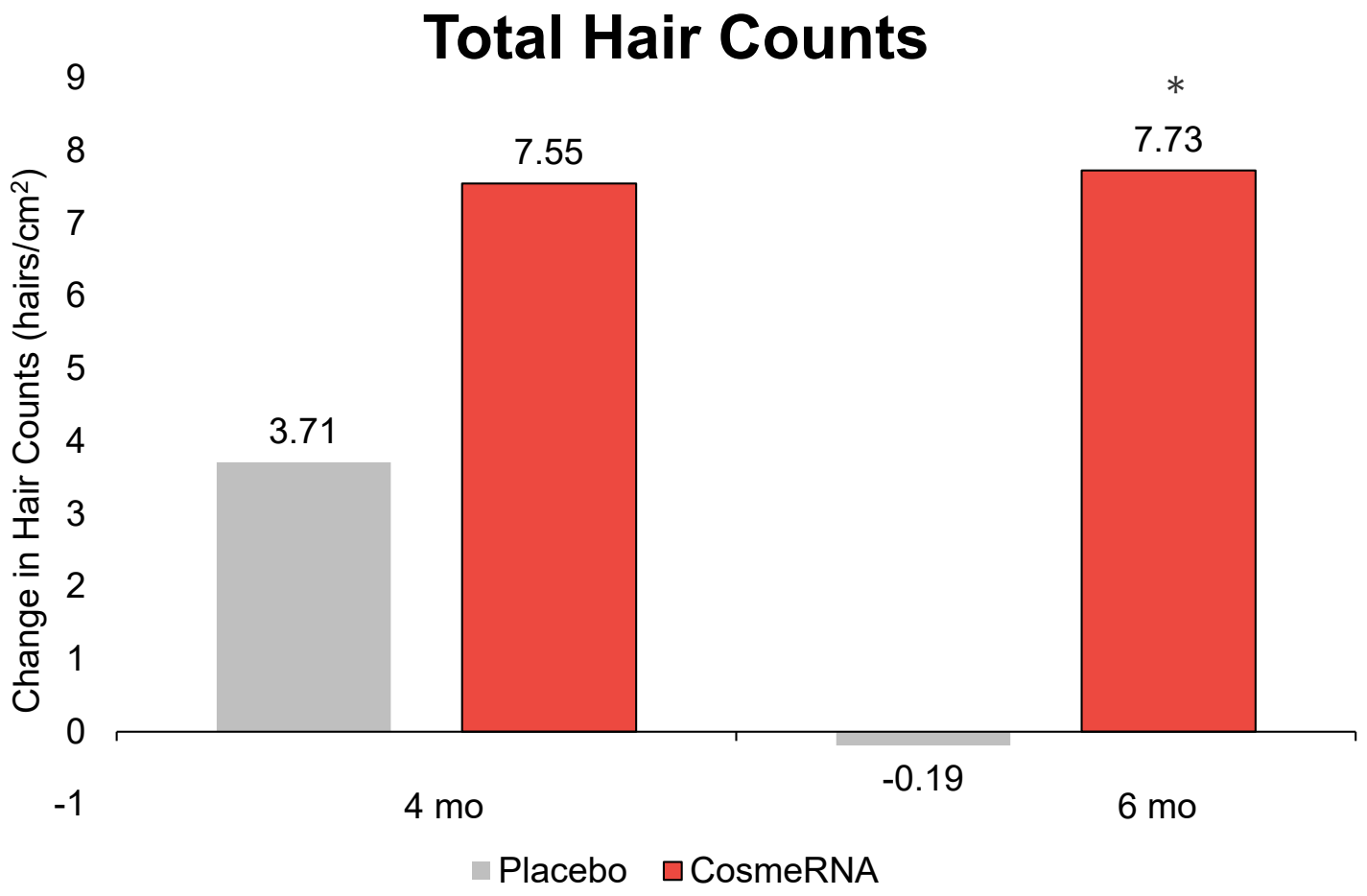
16 weeks	7.545 ± 7.896	3.714 ± 10.335	0.279
24 weeks	7.727 ± 8.659	-0.190 ± 12.875	0.026*

Clinical Study in Korea: Study II: Safety & Efficacy of CosmeRNA by Ellead

Demographics

Characteristics		AR 68 5 mg/ml (n=22)	Placebo (n=21)
		n (%)	n (%)
Sex	Male	9 (40.90)	10 (47.62)
	Female	13 (50.10)	11 (52.38)
Age	Mean ± SD	44.77 ± 10.88	46.48 ± 7.93
	Median	49.50	48.00
	Min, Max	22.00, 54.00	25.00, 54.00
	20 <	0 (0.00)	0 (0.00)
	20-29	4 (18.18)	2 (9.52)
	30-39	1 (4.55)	-
	40-49	6 (27.27)	9 (42.86)
	≥ 50	11 (50.00)	10 (47.62)

Clinical Study in Korea: Hair count increased significantly with weekly application

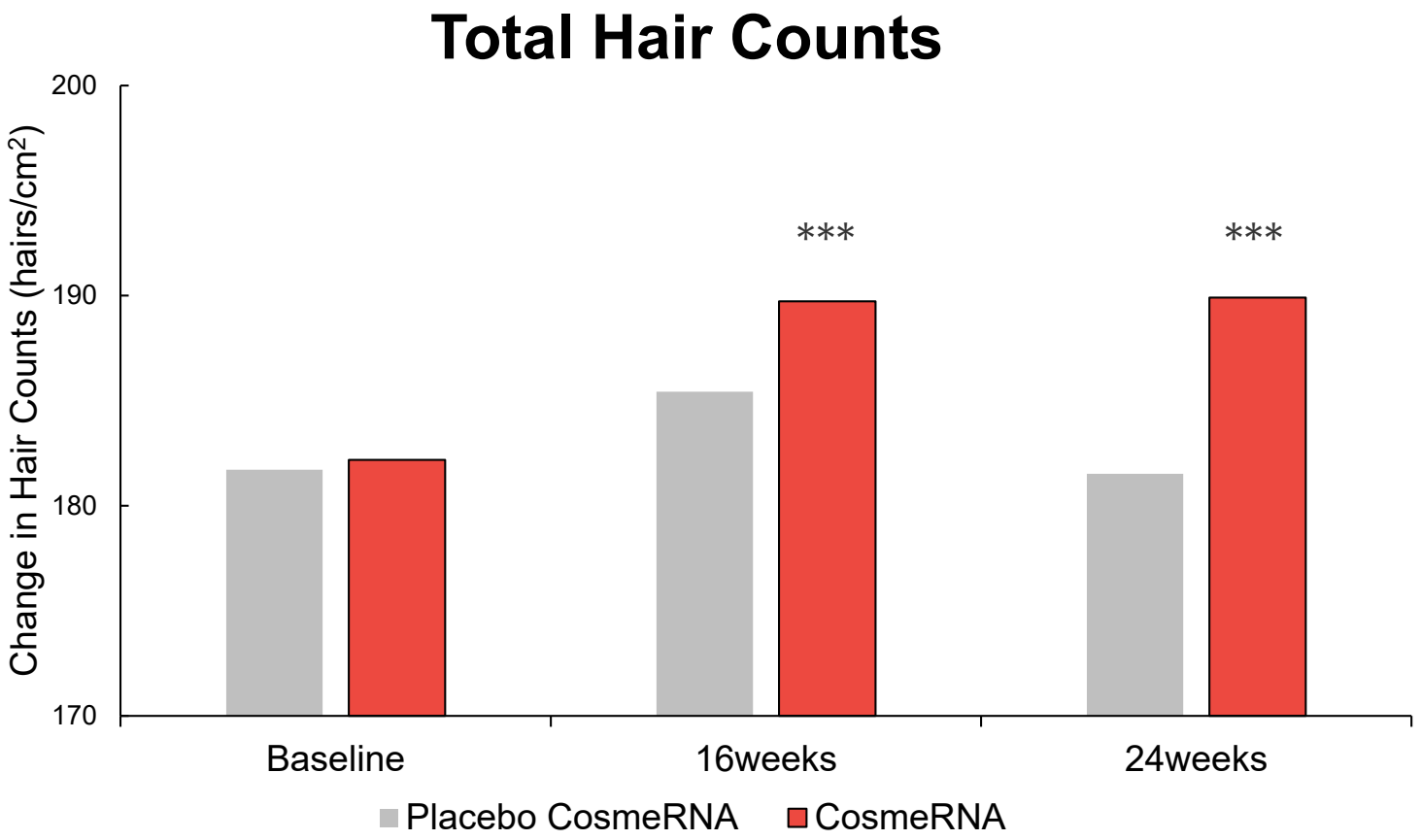


	Placebo (n=21)	Cosmerna 5 mg/Ml (n=22)
♂	9	10
♀	13	11

Yun, SI., Lee, SK., Goh, EA. et al. Weekly treatment with SAMiRNAtargeting the androgen receptor ameliorates androgenetic alopecia. Sci Rep 12, 1607 (2022). https://doi.org/10.1038/s41598-022-05544-w

All subjects placed their head into a hair photograph device (Canfield Scientific), and photographs were taken at fixed distance, angle and lighting with an EOS Rebel T6i digital camera (Canon). Global evaluation was performed by comparing clinical images at baseline with those at 8, 16 and 24weeks after treatment with the test product. The investigator qualitatively assessed clinical images on a 7-point scale (− 3, marked decrease; − 2, intermediate decrease; − 1, slight decrease; 0, no change; + 1, slight increase; + 2, intermediate increase; and + 3, marked increase).

Clinical Study in Korea: Hair count increased significantly with weekly application

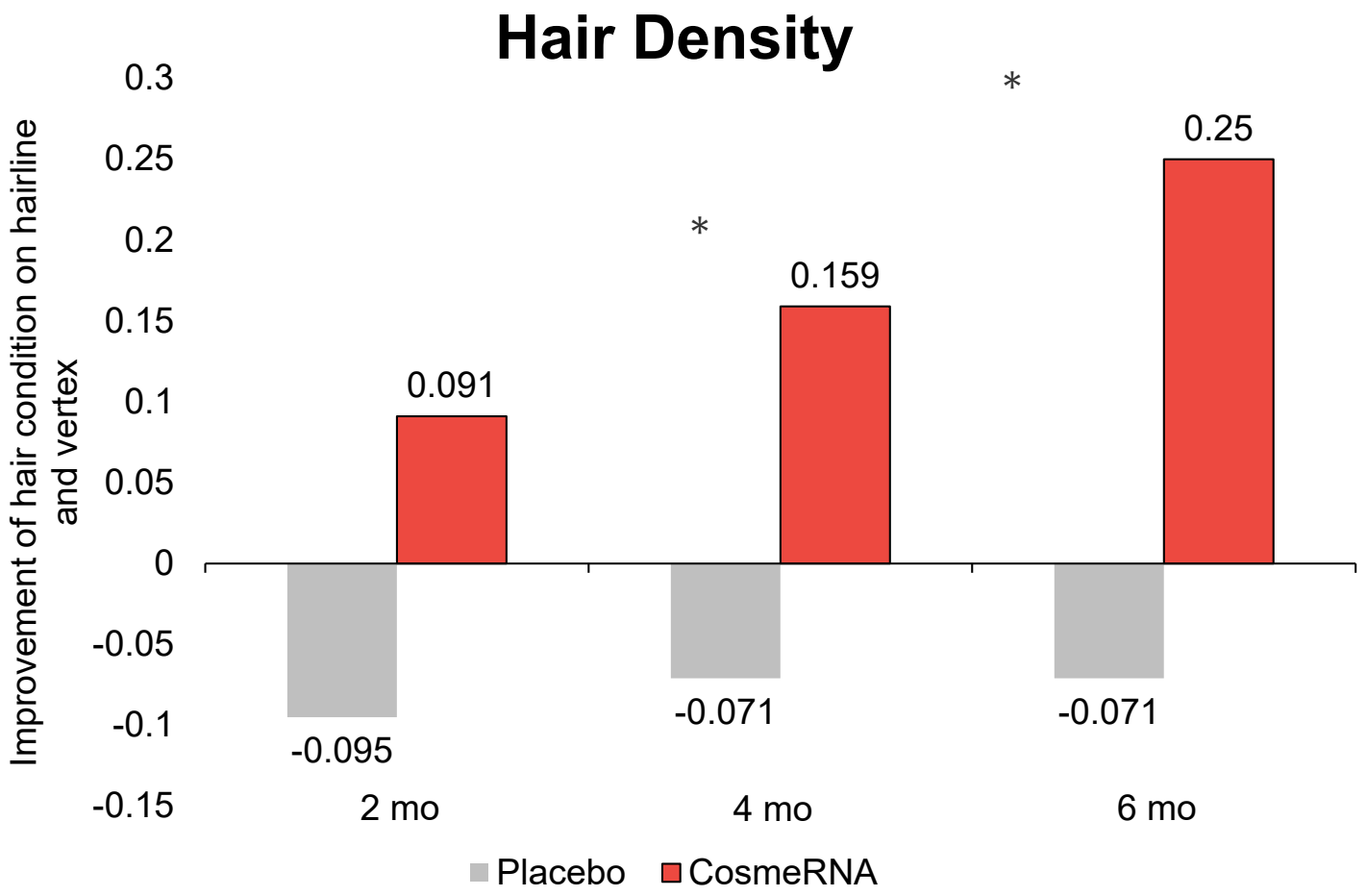


	Placebo (n=21)	Cosmerna 5 mg/Ml (n=22)
♂	9	10
♀	13	11

Yun, SI., Lee, SK., Goh, EA. et al. Weekly treatment with SAMiRNAtargeting the androgen receptor ameliorates androgenetic alopecia. Sci Rep 12, 1607 (2022). https://doi.org/10.1038/s41598-022-05544-w

For evaluation of total hair counts, the hair was clipped approximately 2 mm after a red spot tattoo in the evaluation area (1 cm2) of the hair loss region (forehead hairline or vertex). The total hair counts were assessed using a Folliscope® 2.8 phototrichogramsystem (magnification 14 times, LeadM) at baseline and at 16 weeks and 24 weeks after treatment. The total hair count (number/cm2) was calculated as the number of hairs within an area.

Clinical Study in Korea: Hair density increased significantly within 2 months of application



	Placebo (n=21)	Cosmerna 5 mg/Ml (n=22)
♂	9	10
♀	13	11

Yun, SI., Lee, SK., Goh, EA. et al. Weekly treatment with SAMiRNAtargeting the androgen receptor ameliorates androgenetic alopecia. Sci Rep 12, 1607 (2022). https://doi.org/10.1038/s41598-022-05544-w

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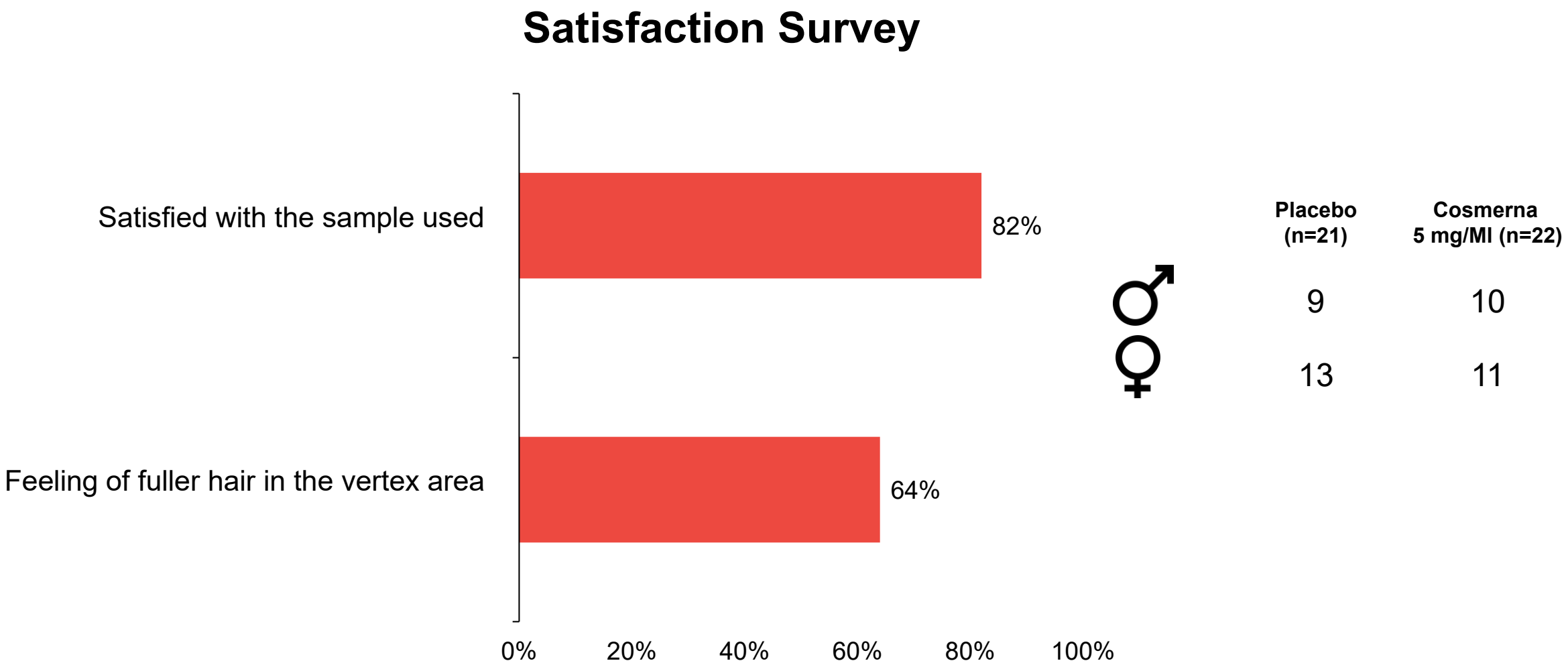
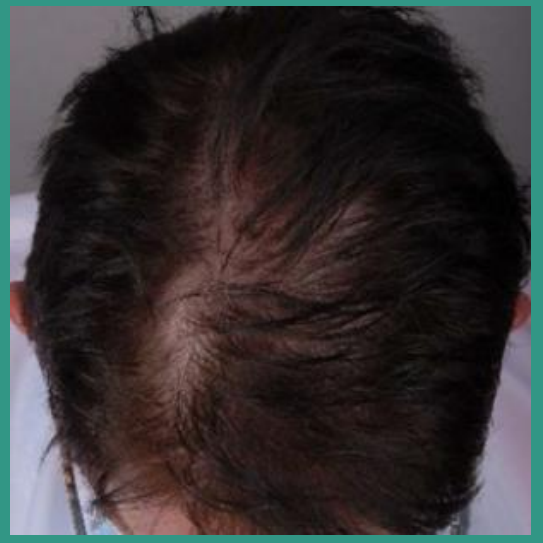
Clinical Study in Korea: High user satisfaction with feeling fuller hair



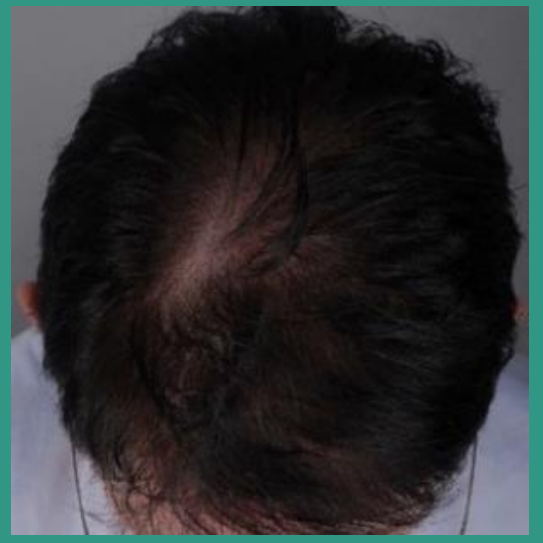
Visible improvement – demonstrated in weekly and monthly applications

BEFORE

AFTER 6 MONTHS



BEFORE



AFTER 6 MONTHS

COSMERNA® Anti-AGA RNA Tonic

6ml- for 3month of supply

•A promising AGA solution by cutting-edge RNA technology
Leveraging out our core competencies in molecular biology since 1992

• Clinically proven efficacy, published on a Scientific report
7.5 / 1cm^2 increase of hair strands in 4 months, Ellead Skin&Bio Research

• Safe mechanism for both of men and women
Precision Targeting of AR mRNA in dermal papilloma cells

• Proven safety by no adverse effect
Dermatest certified

•User convenience
Once per two weeks

Key Ingredients
COSMERNA (STEARYLDISULFIDEHEXYL DNA-2-PEG-45/SH-RNA-1
MENTHOL, BIOTIN,:PANTHENOL:

Patent & Certification

Innovation & Best Quality

Listed on PCPC
& Korea Cosmetic Association

Personal Care Products Council

K·C·A 대한화장품협회

cGMP

ISO 22716
BUREAU VERITAS
Certification

IP Right secured

International Patent
Double-stranded oligo nucleotide structure comprising androgen receptor specific sequences and composition comprising the same for preventing hair loss and hair growth

International and domestic trademark registration

INTELLECTUAL PROPERTY PATENTED

Clinically proven safety & efficacy

Clinically proven Efficacy & Safety

SCIENTIFIC REPORTS

Weekly treatment with SAMiRNA targeting the androgen receptor ameliorates androgenetic alopecia. Sci Rep. 2022 Jan 31;12(1):1607.

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Regulation

CPNP & SCPN notified

COSMETIC PRODUCT NOTIFICATION POTAL CPNP

SCPN
GOV.UK

Thank you!

Contact name: CosmeRNA_Support Team
E-mail: support@cosmerna.com