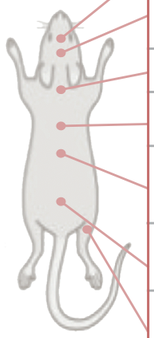
AteloGene®

Reference

1. Takeshita F, et al. Efficient delivery of small interfering RNA to bone-metastatic tumors by using atelocollagen in vivo. (2005) Proc Natl Acad Sci U S A. 102(34):12177-12182.
2. Ogawa S, et al. Influence of systemic administration of atelocollagen on mouse livers: an ideal biomaterial for systemic drug delivery. (2011) J Toxicol Sci. 36(6):751-762.
3. Imamura T, et al. Depleted tumor suppressor miR-107 in plasma relates to tumor progression and is a novel therapeutic target in pancreatic cancer. (2017) Scientific reports. 7(1):5708.
4. Kono M, et al. RasGRP4 is Aberrantly Expressed in the Fibroblast-like Synoviocytes of Patients with Rheumatoid Arthritis and Controls their Proliferation. (2015) Arthritis Rheumatol. 67(2):396-407.
5. Makino K, et al. The Downregulation of microRNA let-7a Contributes to the Excessive Expression of Type I Collagen in Systemic and Localized Scleroderma. (2013) J Immunol. 190(8):3905-3915.
6. Suzuki K et al. Pivotal Role of Carbohydrate Sulfotransferase 15 in Fibrosis and Mucosal Healing in Mouse Colitis. (2016) PLoS One. 11(7):e0158967.

List of Atelocollagen DDS-related reports (Multiple reports are merged into each disease model)

Purple : Local + Systemic
Blue : Local
Red : Systemic



Organ	siRNA/shRNA	miRNA/MIRNA inhibitor	Plasmid DNA・Antisense ODN※1 Decoy・Aptamer
Head and neck, Eye, Oral cavity	Oral squamous cell carcinoma; Choroidal neovascularization; Head and Neck Cancer; Salivary adenoma; Dry eye; Alveolar bone loss	Oral squamous cell carcinoma; laryngeal cancer; Head and neck cancer; Undifferentiated large cell carcinoma; lymphoma; Glaucoma	Corneal injury
Brain, Nerves, Spinal cord	Progressive multifocal leukoencephalopathy; Gioma; Nuroblastoma; Peripheral neuropathy; Hppocampal function; Spinal cord injury; Multiple sclerosis; Status epilepticus	Sciatica; Glioma	Familial amyloid polyneuropathy; Glioma
Respiratory organs	Non-small cell lung cancer; Asthma; Mesothelioma; Lung adenocarcinoma; Lung cancer; Emphysema	Mesothelioma; Pulmonary fibrosis	–
Cardiovascular	Abdominal aortic aneurysm; Endovascular thickening; Intraplaque hemorrhage; Lower extremity ischemia; Hypertension; Vasoconstriction; Ischemia-reperfusion injury	Vascular inflammatory disease; Cardiac hypertrophy; Atherosclerosis; Myocardial infarction; Hypoadiponectinemia	Thoracic aortic aneurysm; Vascular endothelial dysfunction
Digestive organs	Gastric cancer; Hepatocellular carcinoma; Colon cancer; Pancreatic cancer; Bile duct cancer; Colorectal cancer; Esophageal squamous cell carcinoma; Gallbladder cancer; Drug-and chemical-induced liver injury; Alcoholic hepatitis; Acute/chronic colitis	Gastric cancer; Colorectal cancer; Pancreatic cancer; Colon cancer; Esophageal squamous cell carcinoma; Fatty liver	Gastrointestinal cancer; Gastric cancer; Rectal cancer;
Genital and urinary organs	Prostate cancer; Cervical cancer; Endometrial cancer; Testicular cancer; Urothelial cancer; Bladder cancer; Ovarian hyperstimulation syndrome; Ovarian cancer; Renal stones; Renal cell carcinoma; Diabetic nephropathy	Prostate cancer; Endometrial Cancer; Bladder cancer; Overactive bladder	Prostate cancer; Testicular cancer
Locomotorium	Amyotrophy; Arthritis; Fracture; Bone differentiation; Osteosarcoma; Ewing's sarcoma; Muscle injury (Muscle regeneration) ;Bone regeneration; Bone metabolism, Glucose homeostasis; Limb-body muscular dystrophy	Arthritis; Refractory fracture; Anterior cruciate ligament injury; Meniscal injury; Medial collateral ligament injury; Achilles tendon injury; Muscle injury (Muscle regeneration); Myosarcoma; Rhabdomyosarcoma; Muscle injury	Rhabdomyosarcoma; Osteoporosis; Osteosarcoma
Skin	Melanoma; Nickel allergy; Fibrosis; Squamous cell carcinoma; Scleroderma; Contact dermatitis; Pressure injury	Scleroderma; Skin homeostasis/Hair cycle	Melanoma; Contact dermatitis
Immunity, Metabolism, etc.	Obesity; Breast cancer; Myeloma; Neuroendocrine tumor; Autoimmune diabetes; Aging; Inflammatory disease; Sepsis	Breast cancer; Fat accumulation; Obesity; Obesity-induced diabetes	Sepsis

※1 ODN: Oligodeoxynucleotide

Comparison table of AteloGene® products

*Research use only

Catalog No.	Product	Formation of complexes with nucleic acids	Method of administration	Gel formation time	Concentration of nucleic acid	Dosing interval	Size
KOU-1492	AteloGene Local Use * "Quick Gelation"	Yes	Local	About 10 min.	0.5-1.0 nmol /administration	Around 1 week	1Kit (15 times ※2)
KOU-1393	AteloGene® Systemic Use	Yes	Intravenous/ Intraperitoneal injection	Without gelation	2.0-4.0 nmol /administration	Around 3 days	1Kit (10 times ※2)

※2 It is calculated as 200 µl/dose, so it may be possible to administer more than the number of doses indicated depending on the target tissue.

World distributor

COSMO BIO USA.

2792 Loker Avenue West, Suit 101, Carlsbad, CA 92010 USA
Phone : +1 760-431-4600 / Fax : +1 760-431-4604
e-mail : support@cosmobiousa.com
web : https://www.cosmobiousa.com/

Please don't hesitate to contact us with any questions related to product selection or use.

https://www.cosmobiousa.com/

生殖器、泌尿器

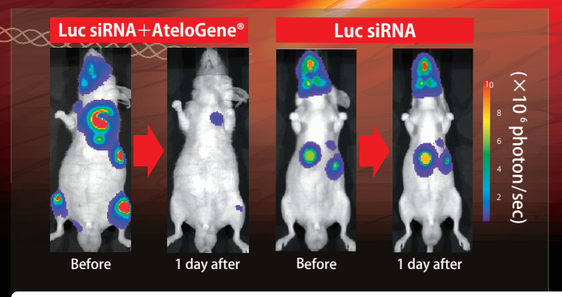
KOKEN

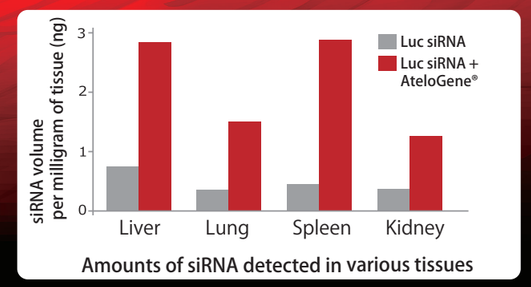
KOKEN

in vivo siRNA/miRNA Transfection Kits

AteloGene®

Local Use & Systemic Use





Amounts of siRNA detected in various tissues

AteloGene® efficiently delivers nucleic acids to different organs

With AteloGene® Systemic Use

Inhibition of luciferase expression by Luciferase siRNA

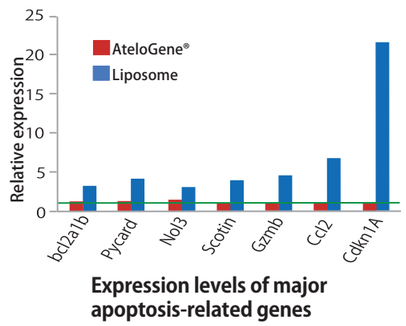
Luciferase siRNA(Luc siRNA)+AteloGene® was administered to a systemic metastatic model of prostate cancer cells stably expressing luciferase via the tail vein, and one day later the imaging device (IVIS) was used to confirm the delivery efficacy of siRNA. Measurements of tissue siRNA levels also confirmed that siRNA was delivered more efficiently to individual organs in the AteloGene®-treated group compared with siRNA alone.

(See Reference 1)

AteloGene® is clearly effective in introducing nucleic acids because of less virulence-induced changes in gene expression

With AteloGene® Systemic Use

Comparison of hepatotoxicity using microarrays



Expression levels of major apoptosis-related genes

Variations in the expression levels of various genes in the liver were analyzed by microarray 24 hours after administration of AteloGene® or Liposome into the tail vein of mice.

AteloGene® treatment group :
The number of genes whose expression level fluctuated or the fluctuation range were obviously little in comparison with the Liposome administration group, and it was shown that AteloGene® was suitable for the in vivo nucleic acid introduction.

Liposome treatment group :
Expression levels of apoptosis-related genes, such as Cdkn1A and Ccl2, and genes associated with biostimulatory / defensive / viral / stress / immune / wound responses were varied, suggesting high virulence.

(See Reference 2)

in vivo siRNA/miRNA Transfection Kits

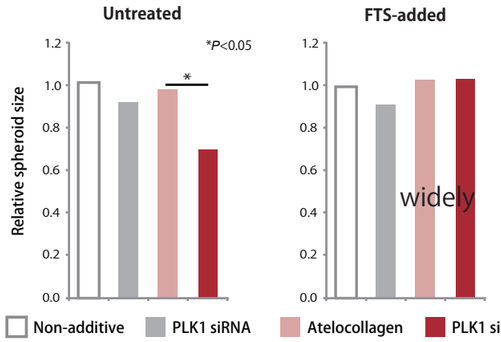
AteloGene® Local Use & Systemic Use

Characteristics of AteloGene®

- **Forms Complexes with nucleic acids to protect nucleic acids from degradation**
- **Suppresses immune response to double-stranded RNA**
- **Less variation in gene expression due to toxicity and clear nucleic acid transfer effects**
- **Possible to select either "Local Use -Quick Gelation-" for sustained release of nucleic acids from gels or "Systemic Use" for whole body delivery without gels.**

Atelocollagen, the major component of AteloGene®, forms complexes suitable for in vivo transfer by mixing nucleic acids in appropriate concentrations and proportions. The complexes prevent the degradation of nucleic acids by nucleolytic enzymes and is efficiently introduced into tissue cells by *in vivo*. AteloGene®Local Use -Quick Gelation(QG)- for topical administration retain nucleic acids at the site of administration because of their *in vivo* gelation properties, resulting in sustained release. On the other hand, the AteloGene® Systemic Use for systemic administration is designed to prevent the formation of gels and thus delivers nucleic acids efficiently to the bloodstream through the tail vein.

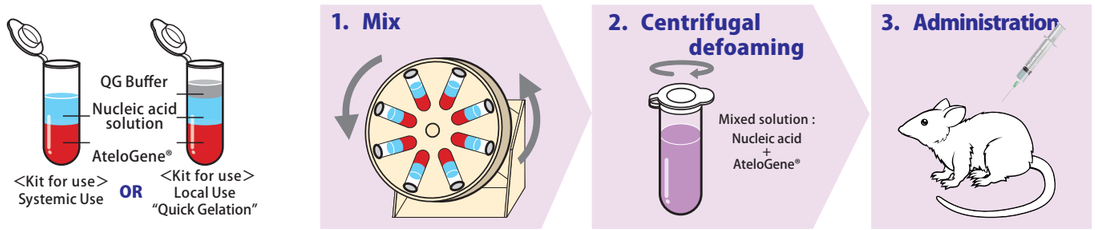
Mechanism of Nucleic Acid Delivery by Atelocollagen



An in vitro model was established using spheroid cultures of non-small cell lung cancer (H1299) cells, into which PLK1 siRNA was introduced to evaluate its proliferation-inhibitory effect. Pre-treatment with various endocytosis inhibitors was performed, and the group treated with a macropinocytosis inhibitor Farnesyl thiosalicylic acid (FTS) showed a reduced effect of PLK1 siRNA compared to the untreated group. These findings suggest that the complex of atelocollagen and nucleic acid is internalized by cells via macropinocytosis. (Internal data)

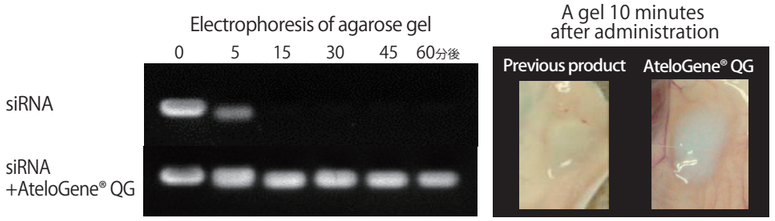
How to use

The preparation of AteloGene® is very simple. A mild mix of the nucleic acid solution with the AteloGene® solution can be administered immediately, with a concentration of 0.5 - 1.0 nmol for topical administration and 2.0 - 4.0 nmol for systemic administration.



AteloGene® protects nucleic acids; for local administration, it gels quickly and releases nucleic acids slowly.

Gel formation in subcutaneous mice and protective effect against nucleolytic enzymes

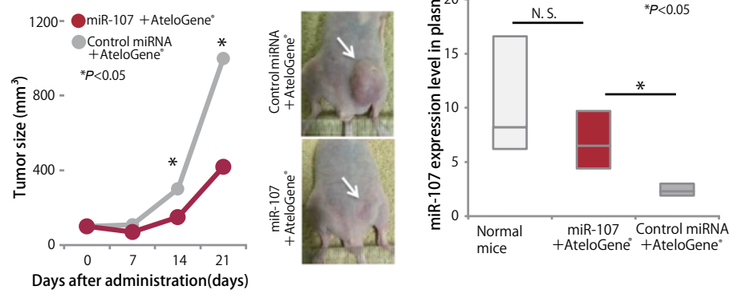


The degree of nucleic acid degradation was confirmed over time at 37℃ after adding RNase to siRNA only and siRNA+AteloGene® QG groups, respectively. Consequently, degradation by RNase was markedly suppressed in the group of mixed solution of AteloGene® QG (left-hand panel). In addition, AteloGene® QG formed a gel more rapidly after subcutaneous injection in mice compared with the conventional product (right figure). (in-house data)

AteloGene® is widely used in cancer research

Tumor growth suppression by local administration of miR-107

With AteloGene® Local Use



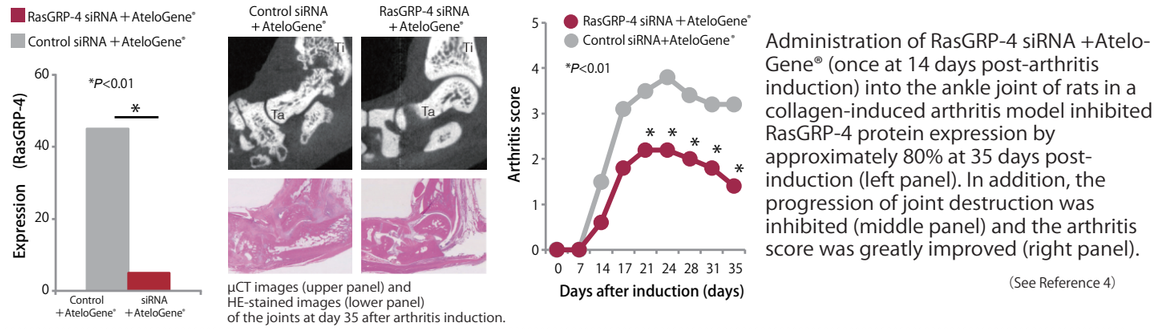
Administration of miR-107 plus AteloGene® (once weekly × 4 times in total) around subcutaneous tumors in pancreatic cancer models resulted in approximately 60% tumor growth inhibition on days 14 and 21 after treatment (left panel). In addition, miR-107, which is repressed in pancreatic cancer patients or mice, increased to levels similar to those in normal mice (right panel).

(See Reference 3)

AteloGene® is also suitable for nucleic acid transfer into joints

Improvement of arthritis with topical RasGRP-4 siRNA

With AteloGene® Local Use



μCT images (upper panel) and HE-stained images (lower panel) of the joints at day 35 after arthritis induction.

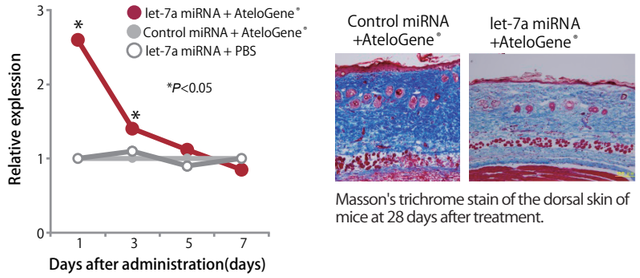
Administration of RasGRP-4 siRNA +AteloGene® (once at 14 days post-arthritis induction) into the ankle joint of rats in a collagen-induced arthritis model inhibited RasGRP-4 protein expression by approximately 80% at 35 days post-induction (left panel). In addition, the progression of joint destruction was inhibited (middle panel) and the arthritis score was greatly improved (right panel).

(See Reference 4)

AteloGene® also helps to introduce nucleic acids into the skin

Inhibition of bleomycin-induced dermal fibrosis by intraperitoneal administration of Let-7a miRNA

With AteloGene® Systemic Use



Masson's trichrome stain of the dorsal skin of mice at 28 days after treatment.

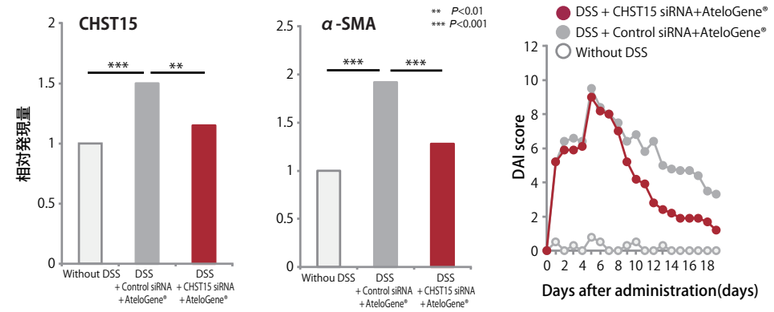
Intraperitoneal administration of let-7a miRNA+ AteloGene® to mice significantly increased the expression of let-7a miRNA in dorsal skin up to 3 days later. Furthermore, intraperitoneal administration of let-7a miRNA+AteloGene® (once weekly × 4 times in total) to mice in a bleomycin-induced scleroderma model inhibited skin thickening and collagen fiber proliferation at 28 days after administration (right panel), demonstrating high nucleic acid transfer efficacy.

(See Reference 5)

AteloGene® also helps to introduce nucleic acids into the digestive system

Amelioration of colitis by intraperitoneal administration of CHST15 siRNA

With AteloGene® Systemic Use



When CHST15 siRNA+AteloGene® was intraperitoneally administered to a dextran sodium sulfate (DSS)-induced colitis model (every 4 days from day 6 after induction × 4 times in total), CHST15 and alpha-SMA expression was suppressed to the same extent as in the non-DSS group on day 19 after induction (left panel, center panel) and disease (DAI) scores were halved (right panel).

(See Reference 6)