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Hyaluronic acid nanogel (HA nanogel)

A New Excipient
Cholesterol substituted hyaluronic acid

New Product Development Office
Functional Additives Div.
Specialty Solutions SBU
Asahi Kasei Co.

What's HA nanogel

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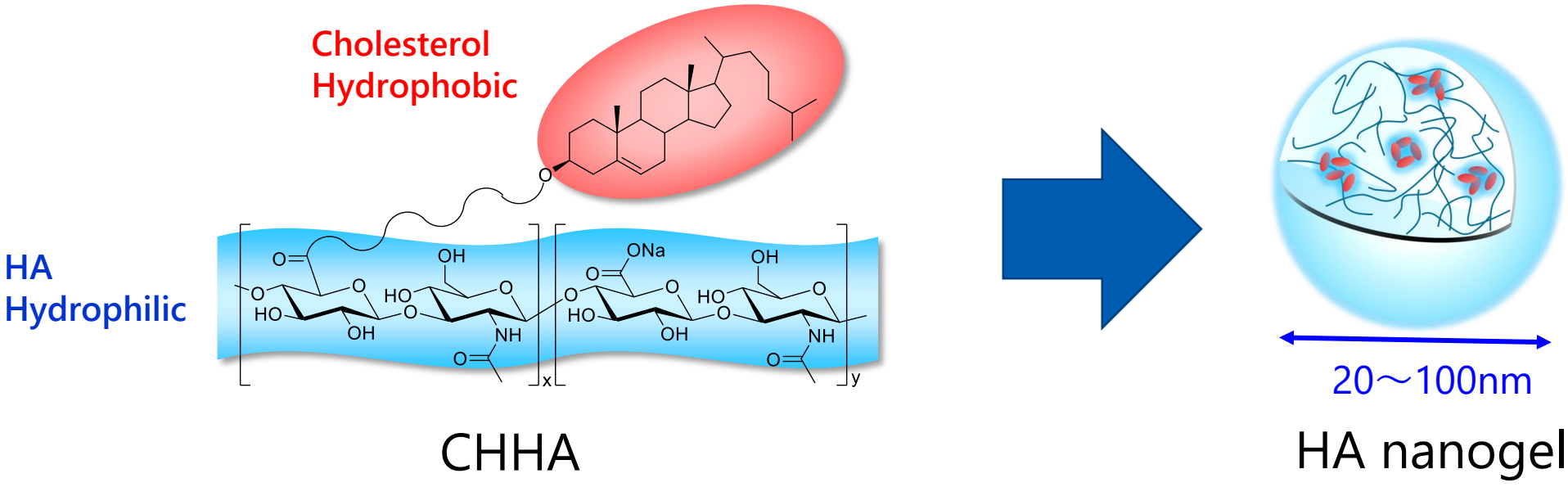
HA nanogel is composed of cholesterol substituted hyaluronic acid (HA), which forms a nano-sized hydrogel particle in water by self-assembly



CHHA

HA nanogel

HA nanogel can host various types of drug molecules via hydrophobic interaction

Technology licensed from Chugai Pharma (WO2010-053140)

Three grades of HA nanogel

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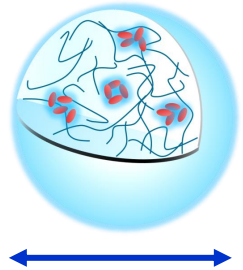
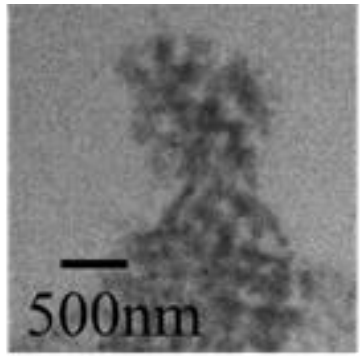
Precipitation Grade:
Precipitated in the subcutis



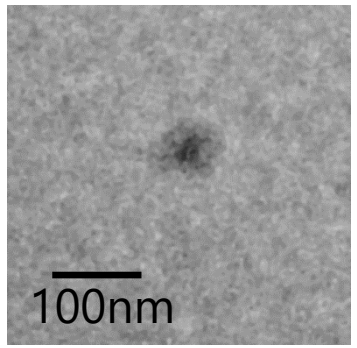
50～100 nm



SC injection

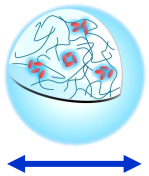
Dispersion Grade:
Circulation in the body

20～50nm

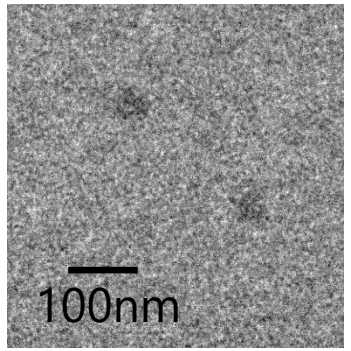


IV injection

Emulsification Grade:
Coating the drug particle



20～50nm



Emulsify the drug

Unique salt-responsive precipitation property

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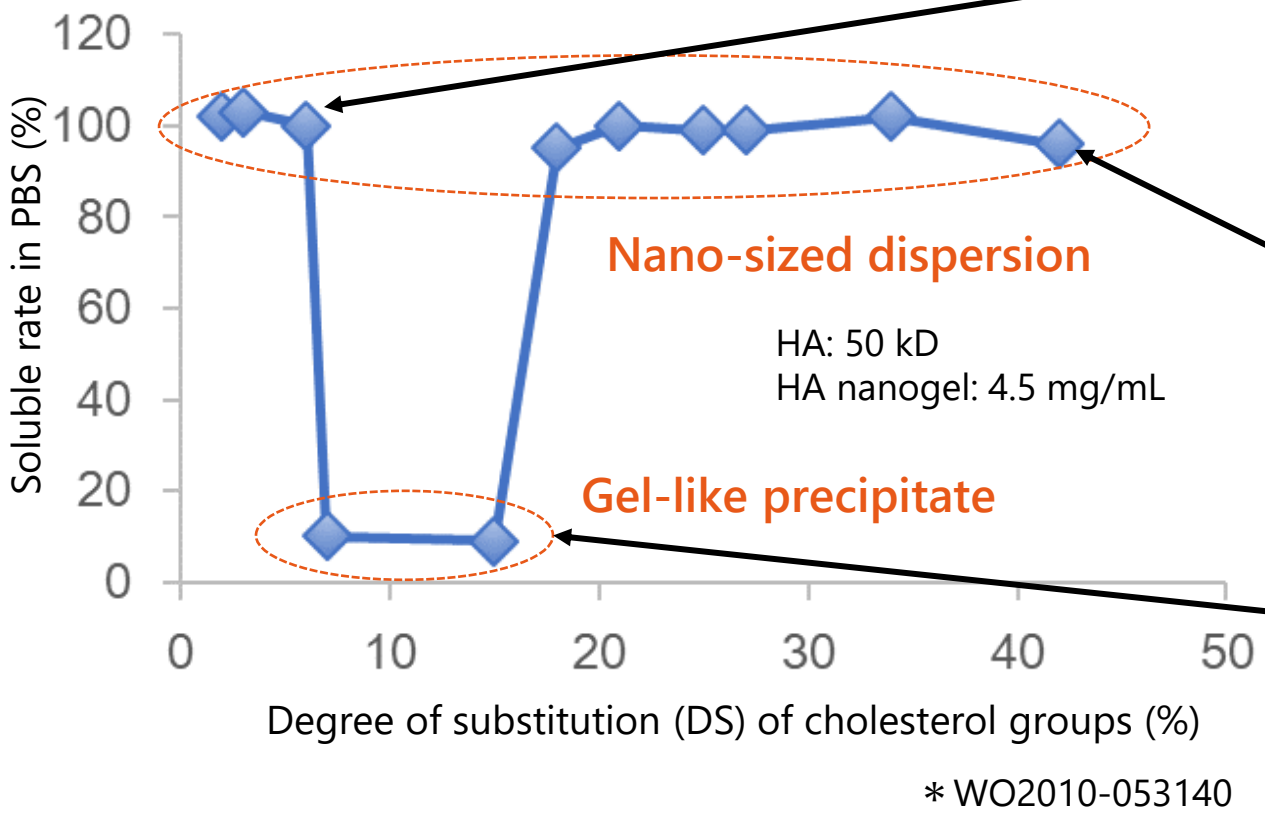
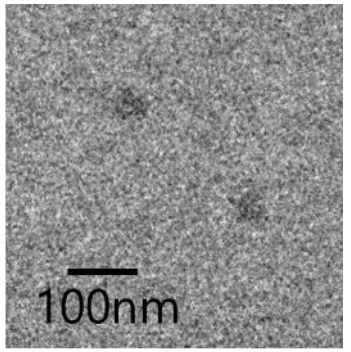
Solubility of HA nanogel in PBS

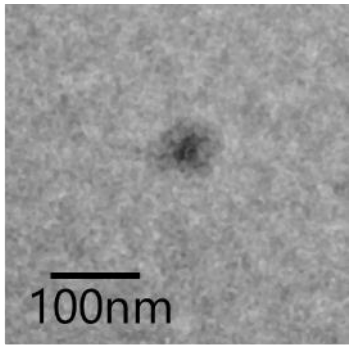


＊WO2010-053140

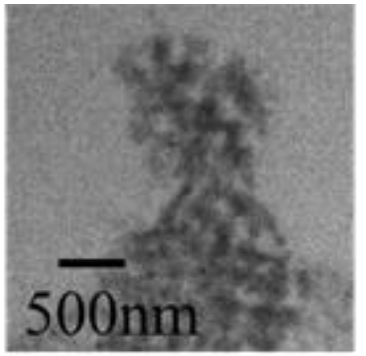
Emulsification Grade
Maintains a stable nano-sized dispersion state in PBS



Dispersion grade
Maintains a stable nano-sized dispersion state in PBS



Precipitation grade
Enables salt-induced precipitation



Grades and main targets

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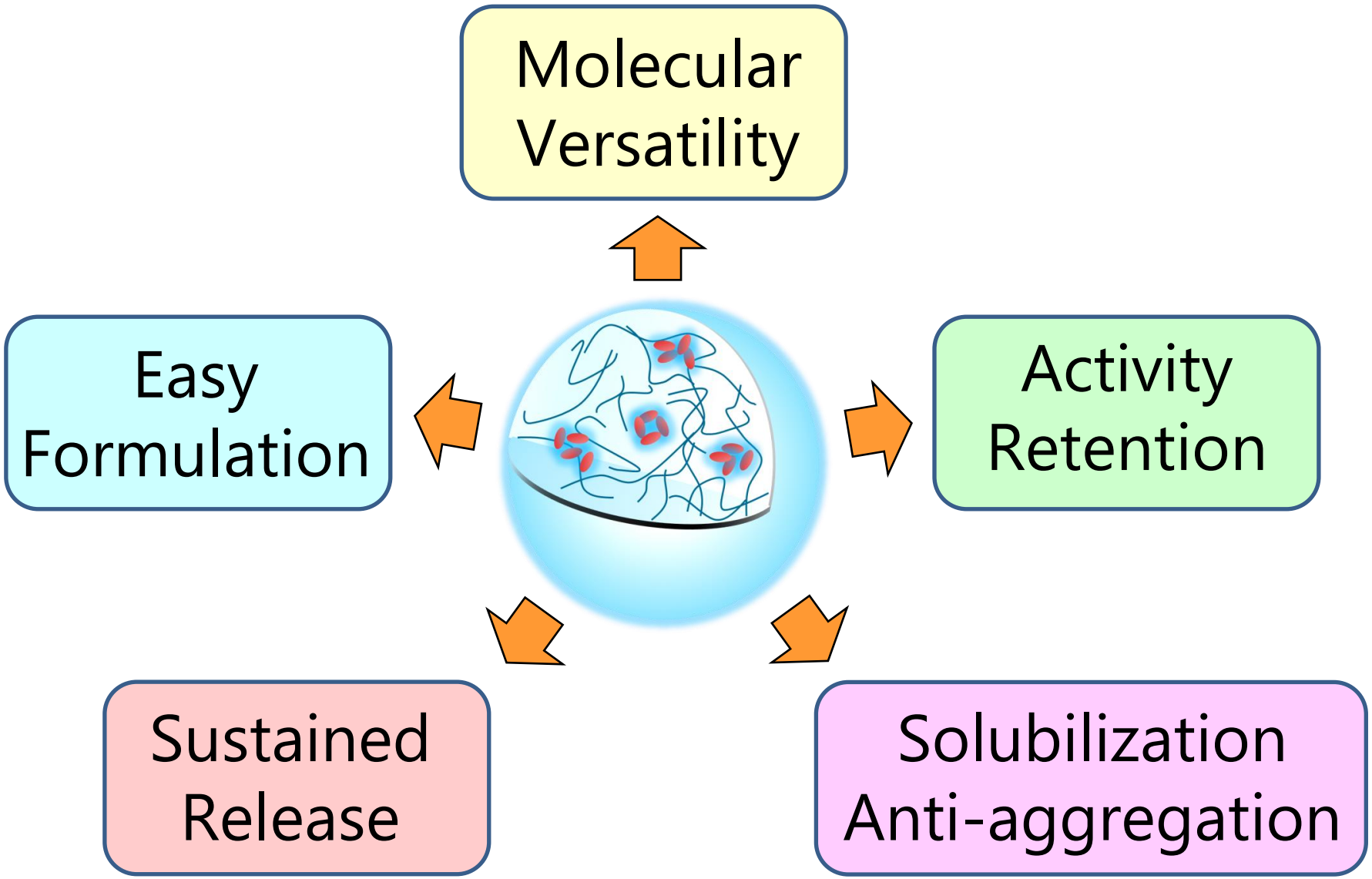
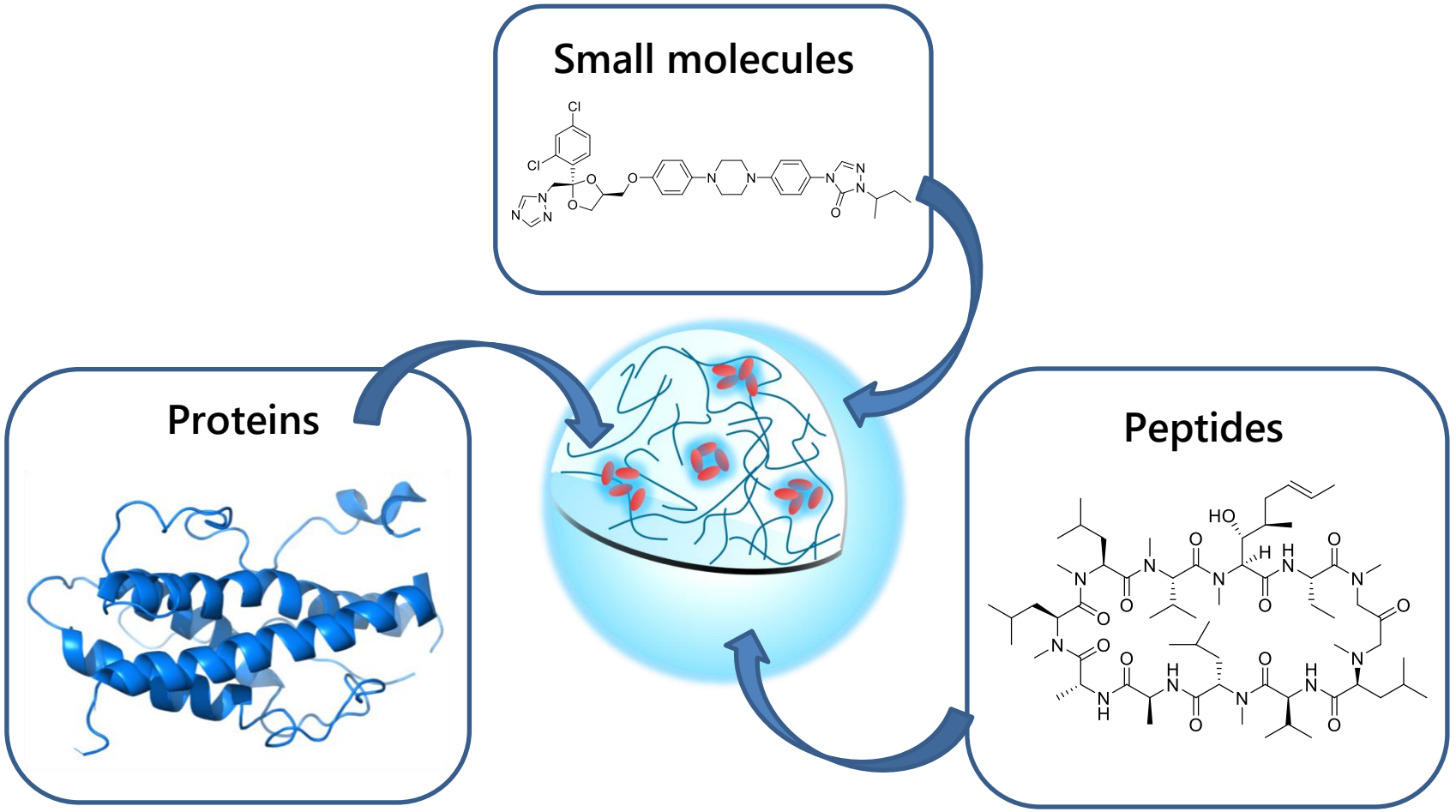
Grade	Emulsification Grade	Precipitation grade	Dispersion grade
Main target	Particle surface coating	Sustained release of biologics	Solubilization of poorly water-soluble drugs
MW of HA	5 – 20 kD	25 – 40 kD	5 – 20 kD
DS of cholesterol	5 – 10 unit mol %	10 – 20 unit mol %	30 – 50 unit mol %
Particle size (PDI)	20 – 50 nm (0.3)	50 – 100 nm (0.3)	20 – 50 nm (0.3)
Expected functions	■ Emulsification of drug particles	■ *In situ* depot sustained release ■ Retained biological activity ■ Inhibition of aggregation ■ High loading capacity (20–40 w/w%)	■ Improvement of solubility ■ Inhibition of aggregation ■ High loading capacity (5–15 w/w%)

Key functions of HA nanogel

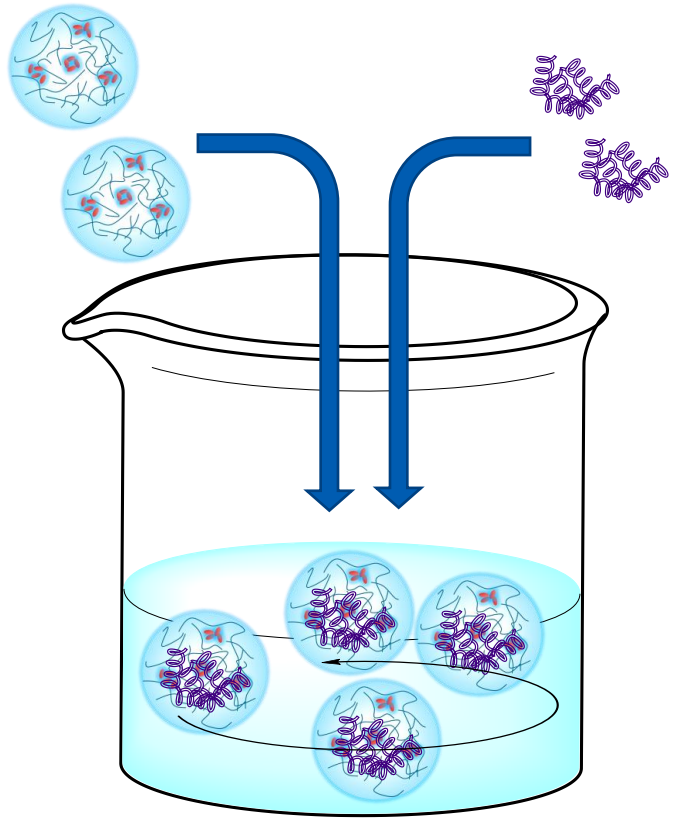


Molecular versatility



HA nanogel can load versatile drug molecules such as proteins, peptides, and small molecules

Easy formulation

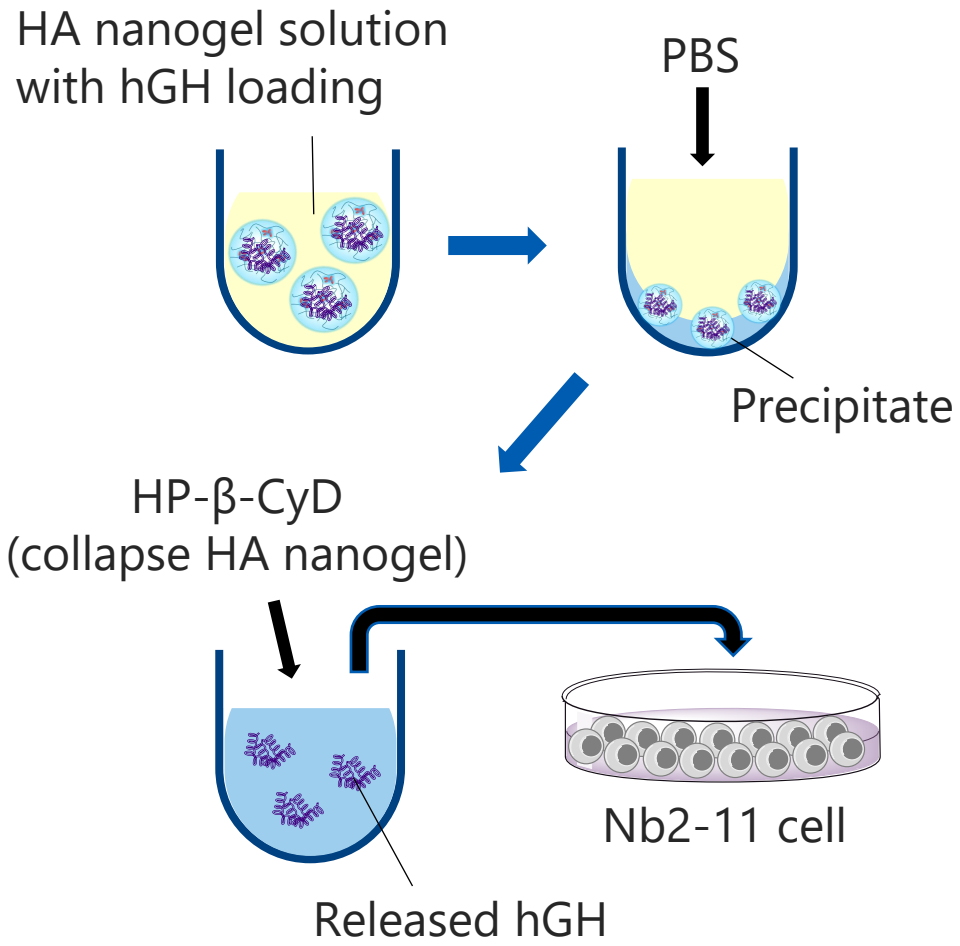


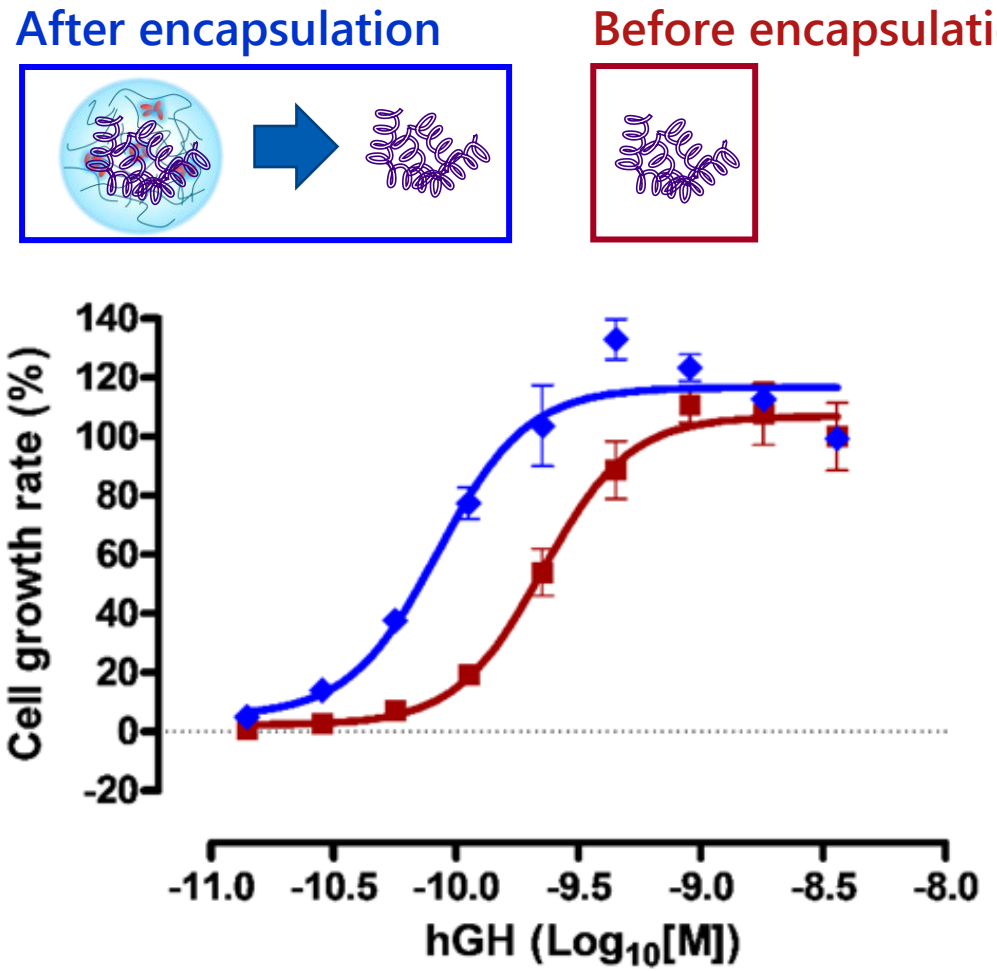
Proteins and peptides	Mw	Loading wt%
Exendin-4	4,200	25*
Lysozyme	14,000	29*
Human growth hormone	22,000	23
Carbonic anhydrase	29,000	26
Erythropoietin	34,000	46*
BSA	68,000	29
Conalbumin	75,000	38
Aldolase	158,000	40

* WO2010-053140

Various drug molecules can be encapsulated by just mixing in water

Activity retention of protein





HA nanogel protects proteins from denaturation while retaining full bioactivity

Sustained release of protein

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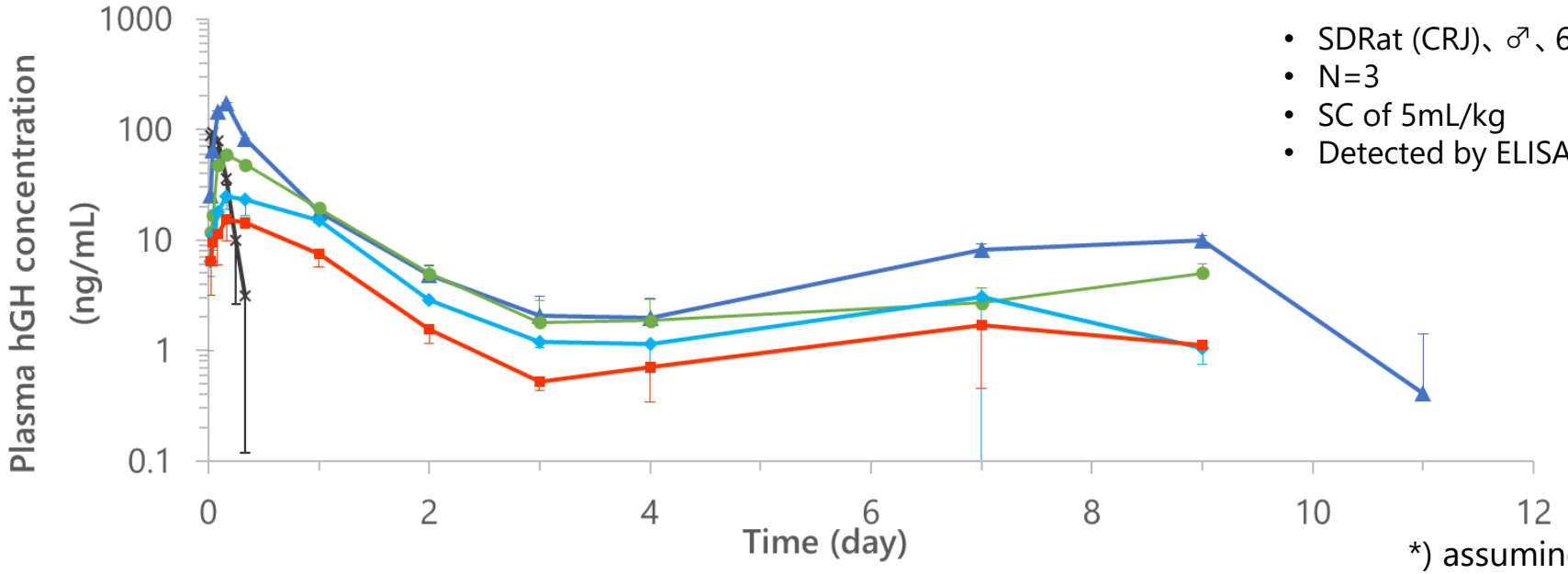
Plasma PK of hGH after SC



*) assuming BLQ=0

Formulation	**hGH**	(mg/kg)	0.5	1.5	3	4.5	6
		(Loading %w/w)	-	5	10	15	20
		(mg/mL)	0.1	0.3	0.6	0.9	1.2
	HA nanogel	(mg/mL)	-	6	6	6	6
PK parameters	**Cmax**	(ng/mL)	99.1	16.8	27.8	58.8	173.2
	AUCinf	(ng hr/mL)*)	332	562	970	1711	2963
	MRTinf	(hr)	2.6	58.4	55.7	53.1	66.3
	BA (vs SC)	(%)	–	58.2	50.3	59.1	76.8

hGH was dose-dependently released for 10 days

Anti-aggregation of protein

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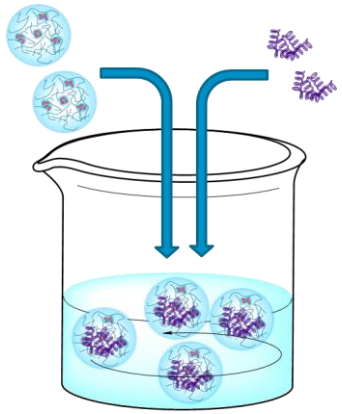
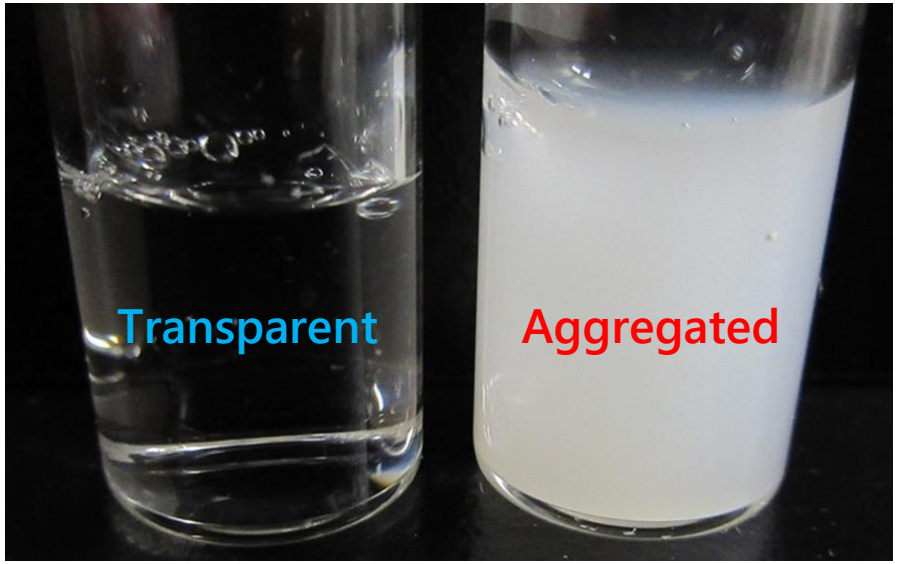
HA nanogel/ Conalbumin
in water
6mg/mL / 2mg/mL

Incubation at 58℃ for 12h

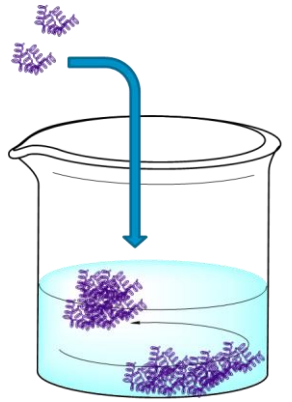
Conalbumin in water
2mg/mL



HA nanogel
+Conalbumin



Same effect detected for both grades



Conalbumin

HA nanogel could protect conalbumin from aggregation caused by thermal denaturation

Solubility enhancement of poorly-water soluble drugs by HA nanogel

Drug	Mw	Solubility (μg/mL)	Solubility with HA nanogel(μg/mL)	Enhanced solubility (times)
Itraconazole	705	<1	3,800	> 3,800
Cyclosporine A	1,202	30	10,000	> 300

Comparison of solubilizing effect of HA nanogel with other solubilizers

Solubility of CyA in solubilizer (50mg/mL)

HA nanogel:	10,000 μg/mL
Cremophor EL:	1,000 μg/mL *
TW80/TW20:	500 μg/mL *
Cyclodextrins:	100 μg/mL *

* AAPS PharmSciTec 2001, 2(1), article 2(http//WWW.pharmscitech.com)

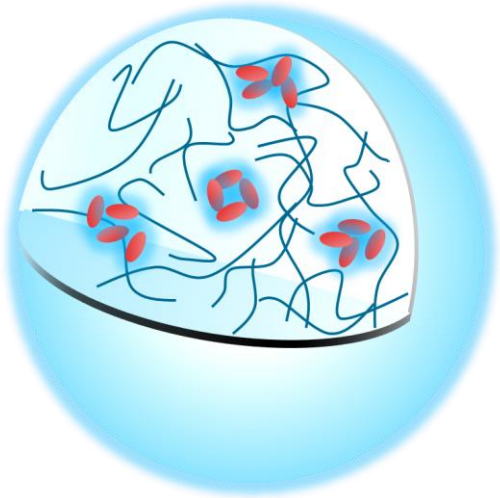
HA nanogel could improve the solubility of poorly water-soluble drugs

Competitive features of HA nanogel

Grade	Precipitation grade	Dispersion grade
Main target	Sustained release of protein/peptide drugs	Solubilization of poorly water-soluble drugs
Competitive features	■ No chemical conjugation necessary (vs. PEGylation) ■ Applicable for protein (vs. PLGA-MS) ■ Easy formulation ■ Aseptic filtration available	■ Higher solubilizing effect (vs. Cremophor EL, TW80/TW20, CyD) ■ Applicable for large molecules (vs. CyD) ■ Safety

Summary

Asahi Kasei has produced a new pharmaceutical excipient, HA nanogel



HA nanogel can

- ✓ load various types of drug molecules by just mixing
- ✓ be used as *in situ* depot sustained release formulation with retained drug activity
- ✓ solubilize and inhibit aggregation of drug molecules

We'd like to develop HA nanogel formulation together with pharmaceutical companies

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Creating for Tomorrow

THE COMMITMENT OF THE ASAHI KASEI GROUP:

To do all that we can in every era to help the people of the world
make the most of life and attain fulfillment in living.
Since our founding, we have always been deeply committed
to contributing to the development of society,
boldly anticipating the emergence of new needs.
This is what we mean by “Creating for Tomorrow.”