VENENO TECHNOLOGIES

The challenge of new drug discovery based on bioactive peptide DRPs (disulfide-rich peptides): the cutting-edge drug discovery platform Veneno Suite™

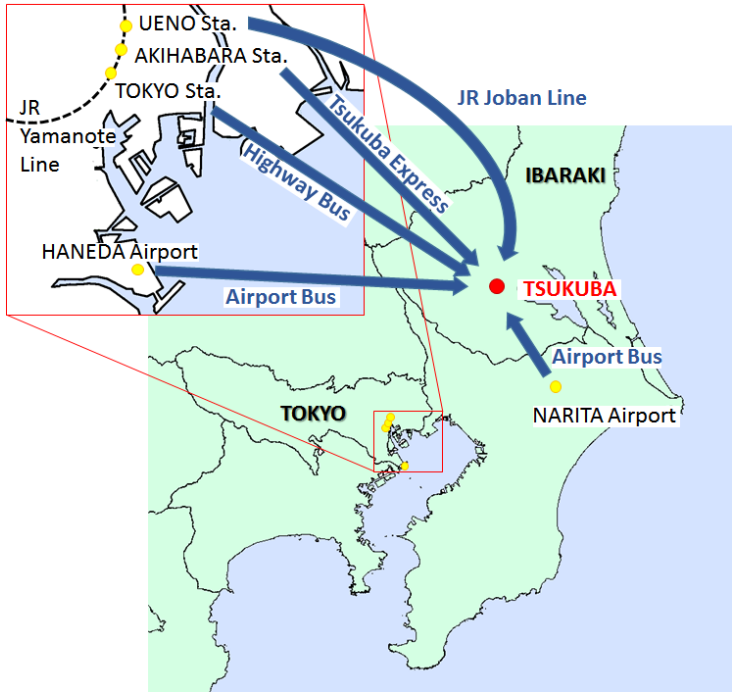
Kazunori Yoshikawa, CEO

Venom-derived therapeutic peptide company

At a glance of Veneno Technologies

About us

- Based in Tsukuba, Japan
- Founded in July 2020
- Focusing on venom-derived therapeutic peptides
- Specialized in venom-derived peptide drug discovery
- PERISS™ technology based on the Evolutionary Molecular Engineering platform using *E.coli*
- Our technology from AIST basic research



The National Institute of Advanced Industrial Science and Technology (AIST), one of the largest public research organizations in Japan,

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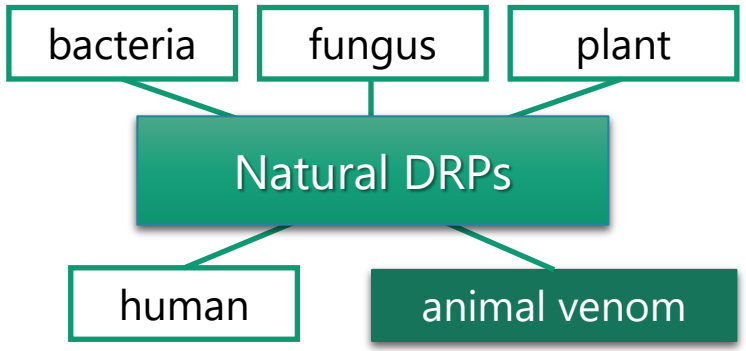
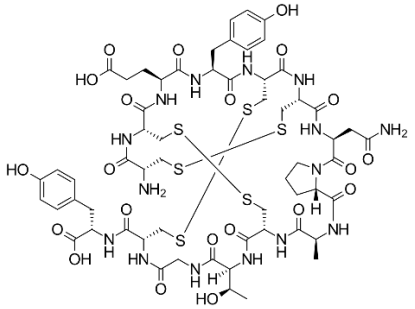
DRP is a bioactive natural peptide

DRP: Disulfide Rich Peptide

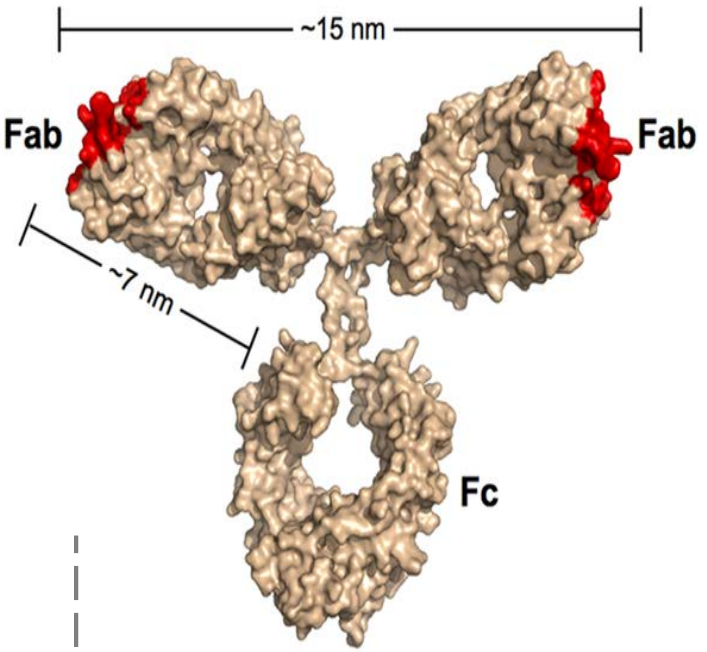


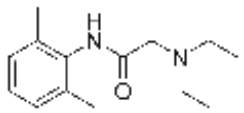


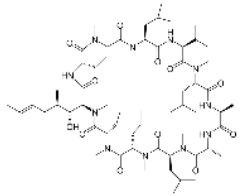
- S-S bonds (>3)
- Rigid folding
- Knot structure

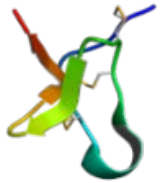
DRPs are widely found in nature

Potent modulator of ion channel and receptor

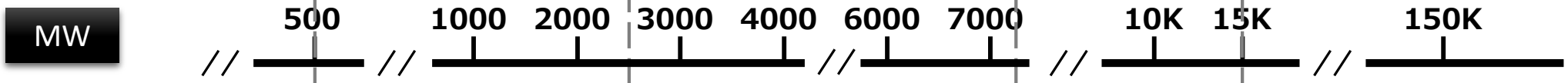








Size: 20 to 60 amino acids



Small molecule (<500 Da)

Cyclic peptide (500 – 2500 Da)

DRP (2.5k - 7k Da)

Antibody (150k Da)

Middle molecule

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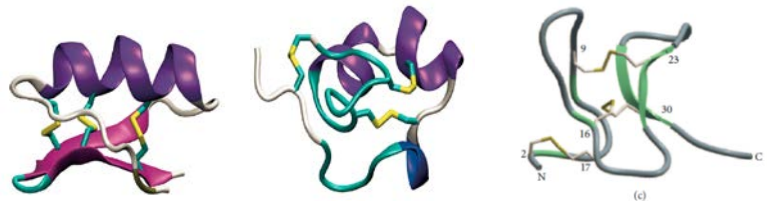
DRP has excellent properties as drug molecule

1. **Natural potent modulator** of ion channels and receptors
   - Animals use DRPs as venom component
   - Plants use DRPs as antimicrobial
2. **Highly selective** to target protein/high subtype specificity
3. **High resistance to proteases**
   - Potential as oral drug targeting intestine
4. **High thermal stability**
   (e.g. GTx1-15 peptide from tarantula is stable at 95C for 24hrs)
   - Benefits in formulation
5. **Low immunogenicity**
6. **Track record as a pharmaceutical product**
   - ✓ Ziconotide (Severe chronic pain, FDA approved in 2004)
   - ✓ Linaclotide (Irritable bowel syndrome, oral, FDA approved in 2012)



scorpion (ChTx) anemone (ShK) tarantula (GTx1-15)

PRIALT (ZICONOTIDE) INTRATHECAL INFUSION

cone snail

Linzess (linaclotide) capsules 72 mcg • 145 mcg • 290 mcg

E. coli enterotoxin

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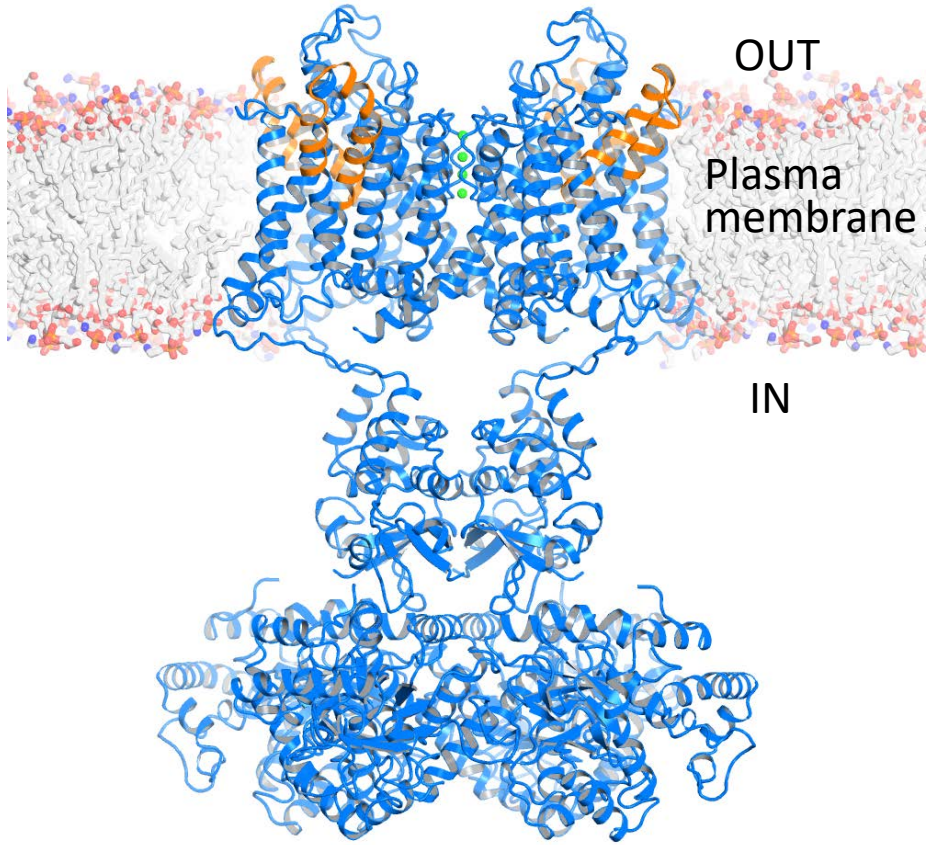
"Ion channels": traditionally important, but difficult targets



Kv1.2-Kv 2.1 paddle chimera tetramer

From: Rockefeller University, Laboratory of Molecular Neurobiology and Biophysics

Ion channels are a major drug target

- ✓ Deeply involved in many diseases
- ✓ One of the most important drug targets
- ✓ Large global market of $12 billion US dollar
- ✓ 80% of channels have remained untouched (240/300 ion channels)

Challenging target class

- ◆ Difficult to express and purify, low stability
- ◆ Limited epitope availability
- ◆ Dynamic molecules with multiple conformations

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Three hurdles to DRP drug discovery

Why research and development of DRP, a natural ion channel agonist, is not going well …

1. Even if venom-derived peptides (DRPs) have been evolved, further molecular engineering would be useful for making drug.
2. No large-scale DRP libraries and robust screening technologies
3. Complex and expensive chemical synthesis of DRPs

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Veneno Suite ™

one-stop technologies for DRP-based drug development

3 core technologies

1) ***DRP Space ™*** :

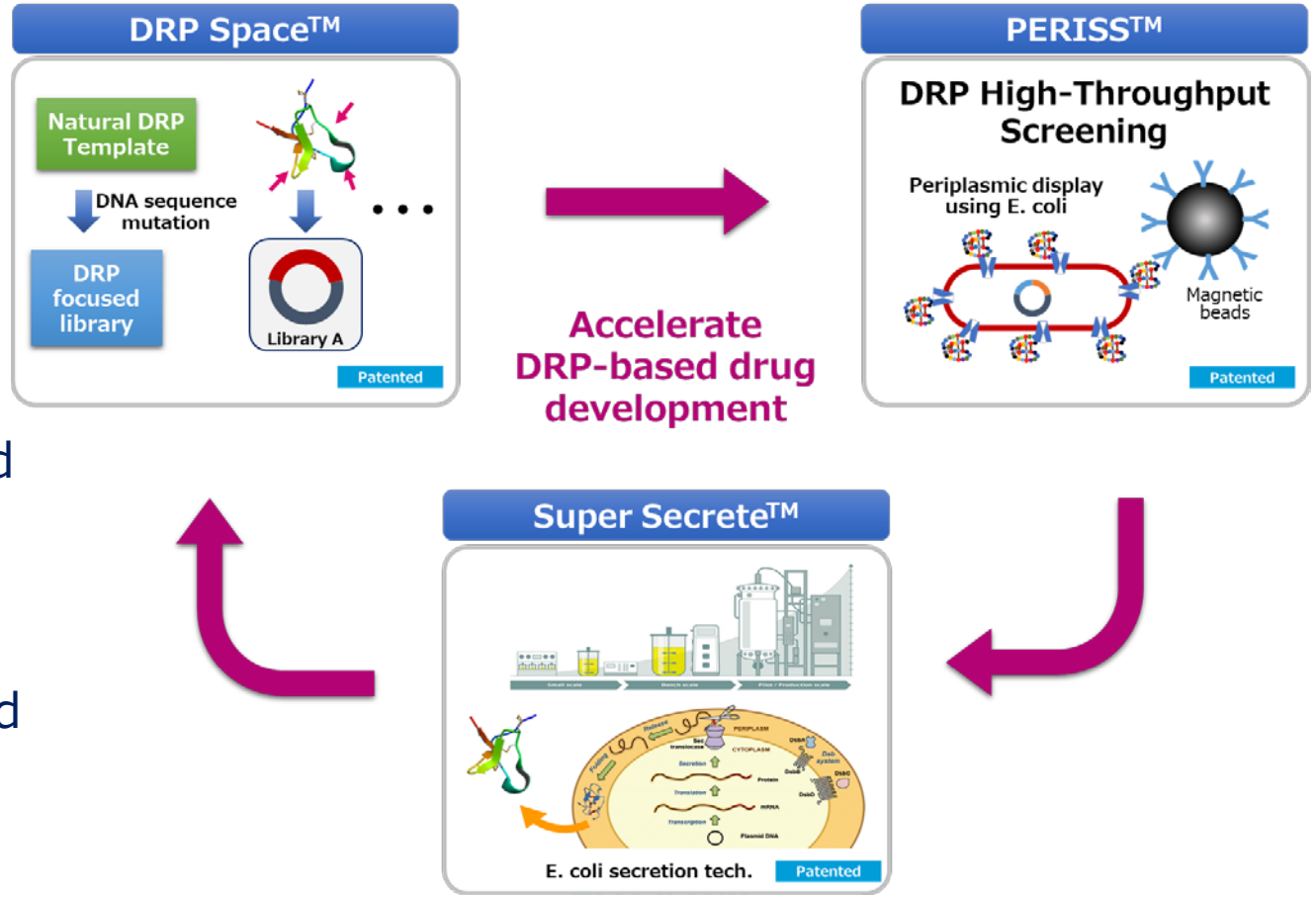
Large size DRP focused library (10^9)

2) ***PERISS ™*** :

High throughput screening technology based on evolutionary molecular engineering

3) ***Super Secrete ™*** :

Low-cost and simple DRP production method using E. coli (from high-mix low-volume to mass production)



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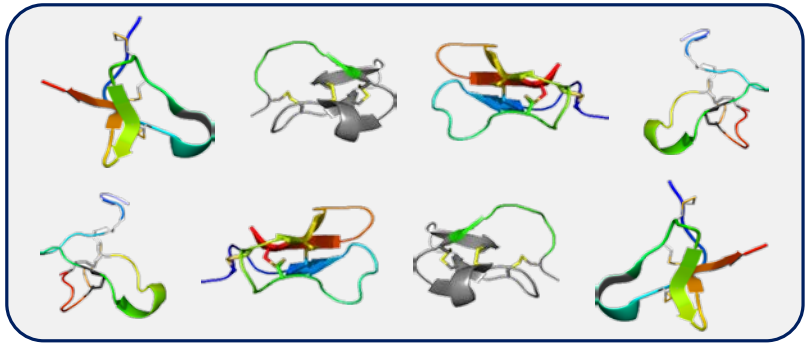
DRP Space™ : Overwhelming DRP focused libraries! (Core 1.)

Conventional DRP libraries

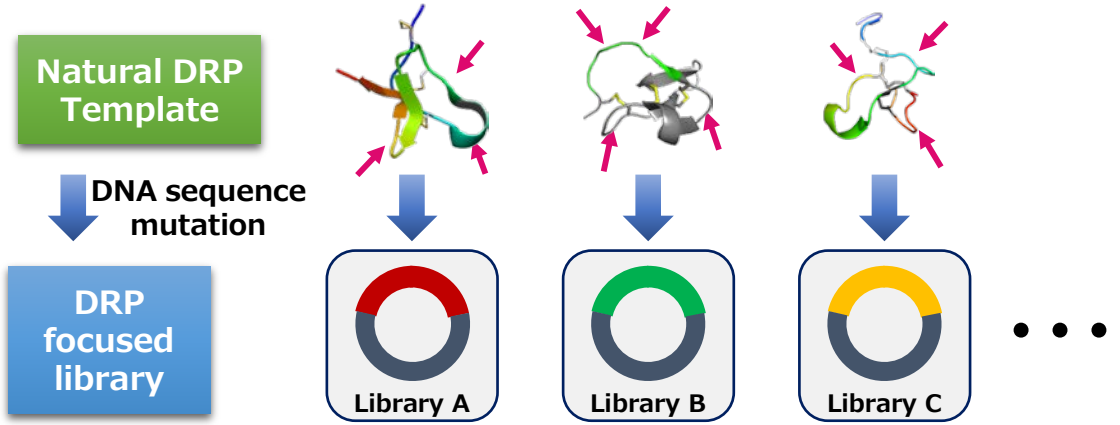
Peptide-based libraries



- Isolated from animal venom or synthetic libraries (chemical or biosynthetic)
- A year to procure organisms (several years for valuable species)
- Several years to create a chemically synthesized DRP library.
- **Library size: limited to around 100**

Our DRP focused libraries

Plasmid-based libraries for PERISS™



- Unique algorithm for mutating DRP DNA sequence
- Library size: 10^9 (billion)
- Biologically active DRP as template, high activity, high selectivity, high probability screening
- Easy to create unique libraries from various natural DRPs

Patented

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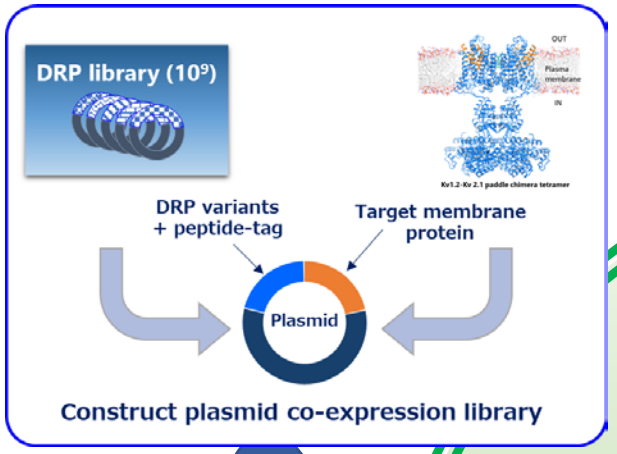
PERISS^{TM} (Periplasm secretion and selection) (Core 2.)



E. coli

Folding

Release

DRP

Periplasmic Display
Selection

PERIPLASM

DsbA

DsbC

DsbB

DsbD

Dsb* formation
system
(enzyme and
chaperone)

* Disulfide bond

Sec
translocase

Secretion

Inner
membrane

DRP

Protein
(cf. Ion Ch.)

Translation

Transcription

CYTOPLASM

Plasmid DNA

Outer
membrane

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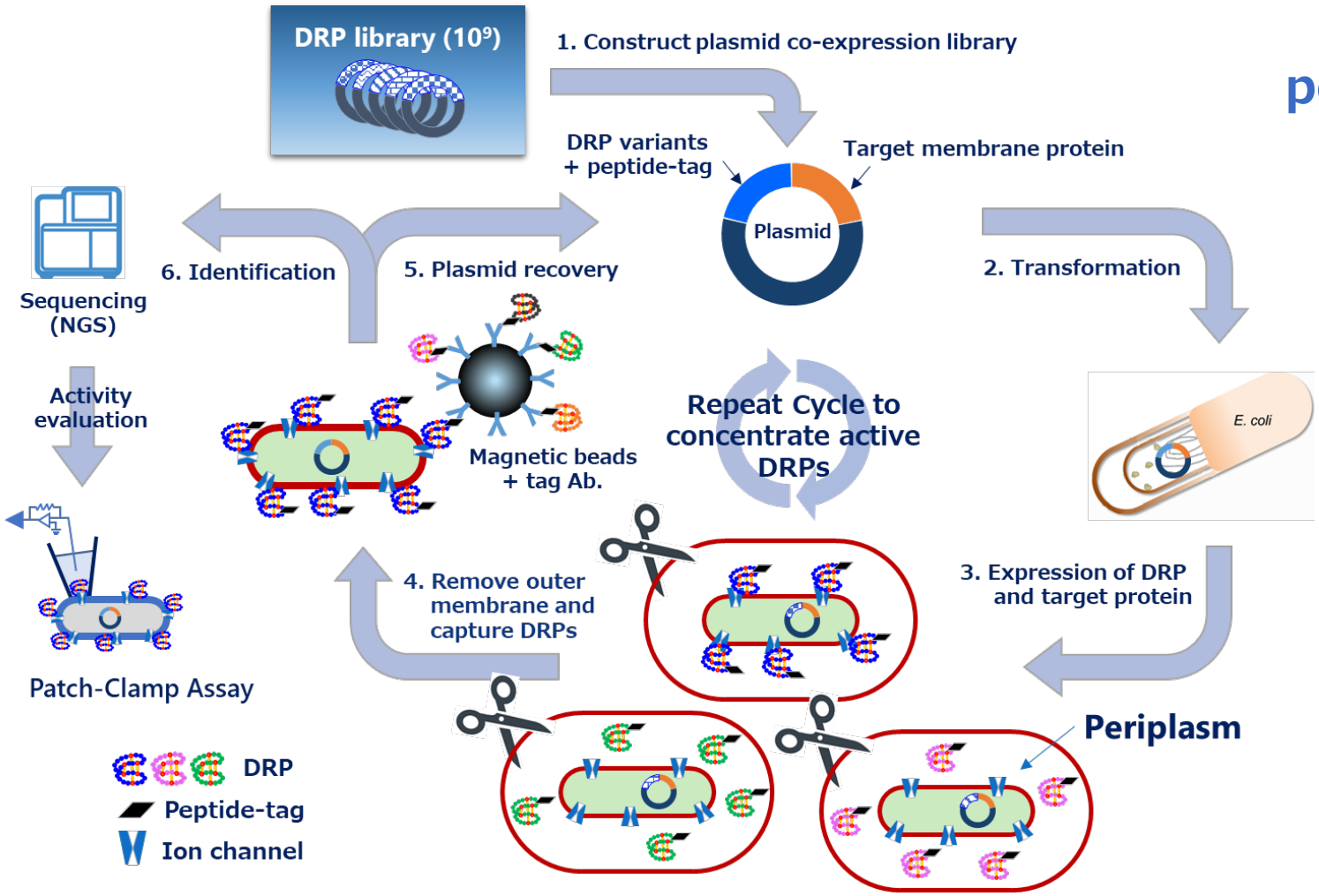
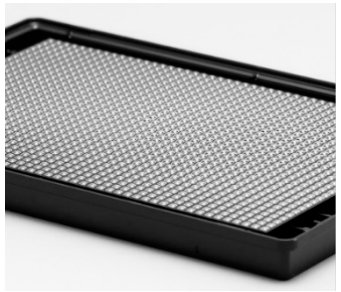
PERISS™ cycle



By repeating the PERISS cycle, peptides likely to act on the target can be obtained efficiently in a short period of time.

PERISS™	Microplate method
	
1 flask (Billions of E. coli)	**500k plates** (1536-well Microplate)

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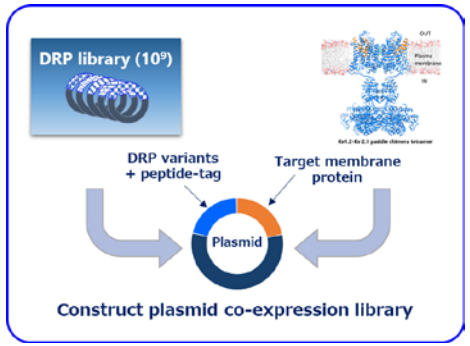
Veneno Suite ™ : one-stop solution for DRP drug development

Huge effort and long years to get hit DRPs from conventional natural/chemical synth. libraries

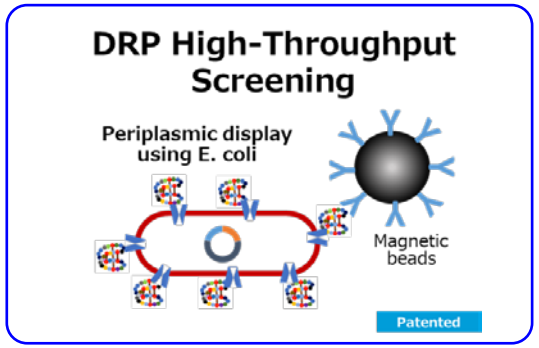
- **Natural/chemical library creation: 1 to several years**
- **DRP identification: 1 to several years**
- **DRP optimization; chemical synthesis of various derivatives and *in vitro* assay: few months per molecule (?) x 10 molecules (?)**

From design to hit DRP 12 months (Best case scenario)

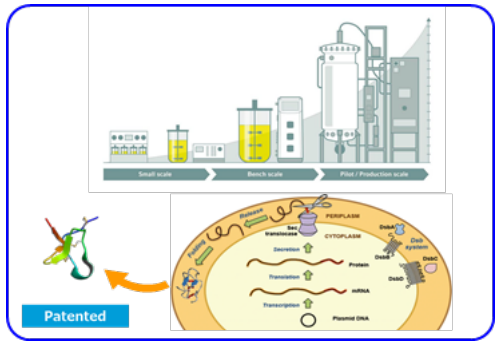
Step 1 : Screening Library



Step 2: PERISS Cycle



Step 3: DRP production



Step 4: in vitro study

DRP library construction (Plasmid-based) → **DRP high throughput screening** (PERISS Cycle) → **DRP production** (from High-mix low-volume to large scale) → DRP activity assessment (electrophysics)

- Inhibitor
- Activator
- Binder

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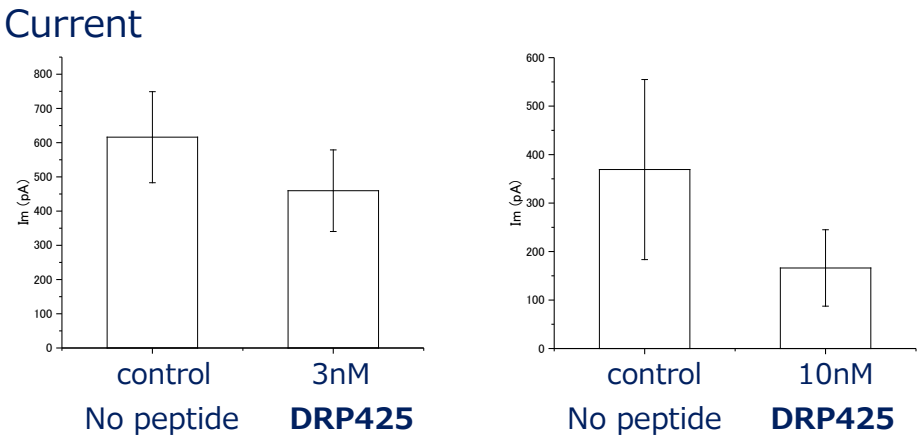
Proof of Concept : TRPV2

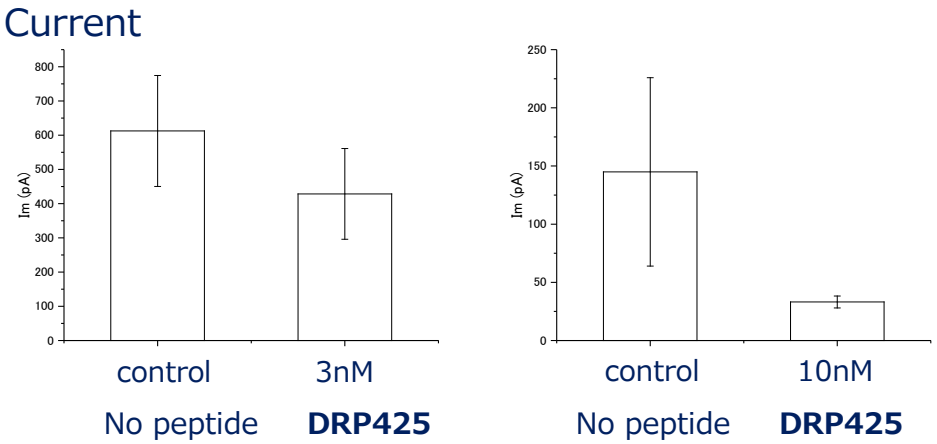
DRP425 inhibits the expression current of TRPV2 channel forcefully expressed in mammalian cells at low concentrations.

HEK293 cell



IC50 of DRP425 is expected to be around 6~7nM

CHO cell



60-80% inhibition of the expression current (at 10nM)

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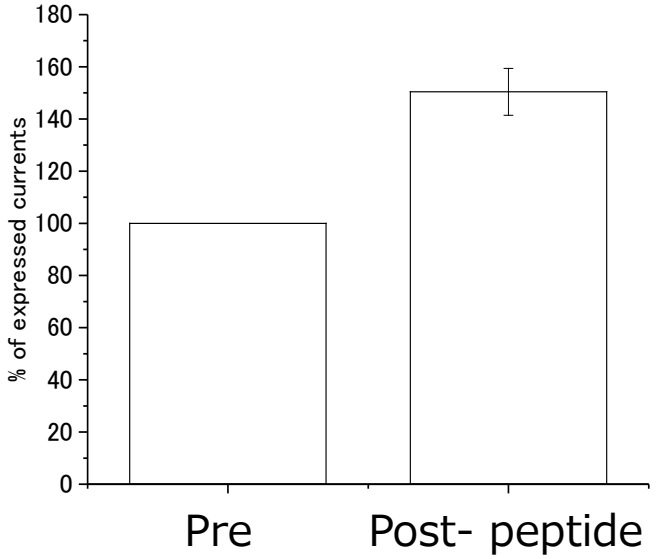
Proof of Concept : TRP**, Kv*.* (two-pore-domain) channels

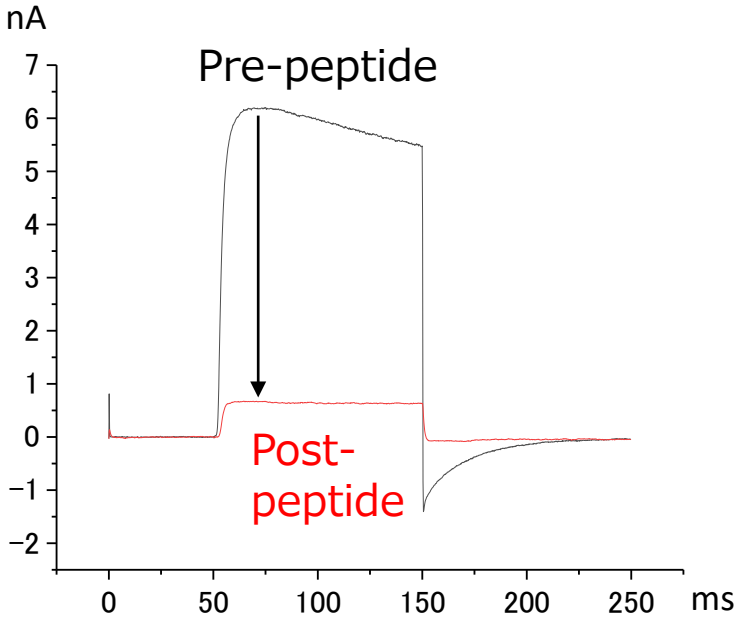
TRP** channel

50% activation at 300 nM
(n=5)

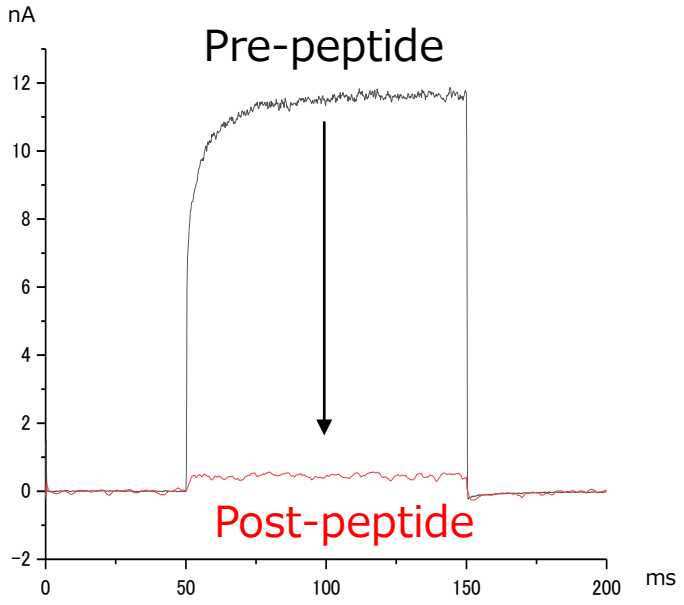


Kv*.* channel (two-pore-domain)

80% inhibition at 60 nM
(n=9)



90% inhibition at 300nM
(n=10)



No ligands have been found yet.

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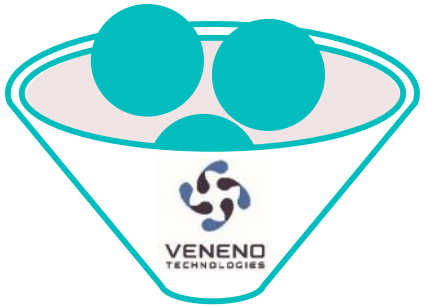
Business Model (Pharmaceutical Business)

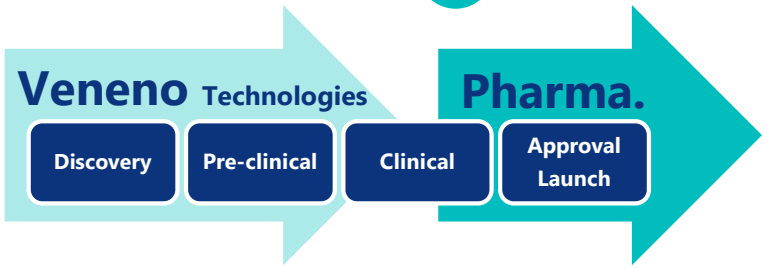
Two business models for advancing DRP drug discovery and development

1: Discovery Partnering
(Discovery Collaboration)



i. License Out
ii. Upfront fee, R&D fee
iii. Milestone payment
iv. Royalty

2: In-House Pipeline
(Strategic development)



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Discovery & Development Current Status

	In-house pipeline	
	Target Channel (type)	Indication (co-research)
On-going (Discovery stage)	**AQP (inhibitor)**	**Brain swelling (Univ.-AMED)**
	Na ch. (inhibitor)	**Pain (Univ.-Kakenhi Grant)**
	K ch. (inhibitor)	**Cancer (VNN)**
In preparation	**Ca ch. (inhibitor)**	**Pain (Company C)**
	CFTR ch. (activator)	**Cystic Fibrosis (bio-venture)**
	CFTR/Cl ch. (activator)	**Myocardial infarction (VNN)**
	Transporter (inhibitor)	**CD, UC, SLE (VNN)**
	MEP (inhibitor)	**MDR bacteria (VNN)**
	Shiga toxin (neutraliz.)	**EHEC (VNN)**

AQP: aquaporin
CFTR: cystic fibrosis transmembrane conductance regulator
MEP: multidrug efflux pump

CD: Crohn's disease
UC: ulcerative colitis
SLE: systemic lupus erythematosus
MDR Multidrug-resistant
EHEC: enterohemorrhagic Escherichia coli

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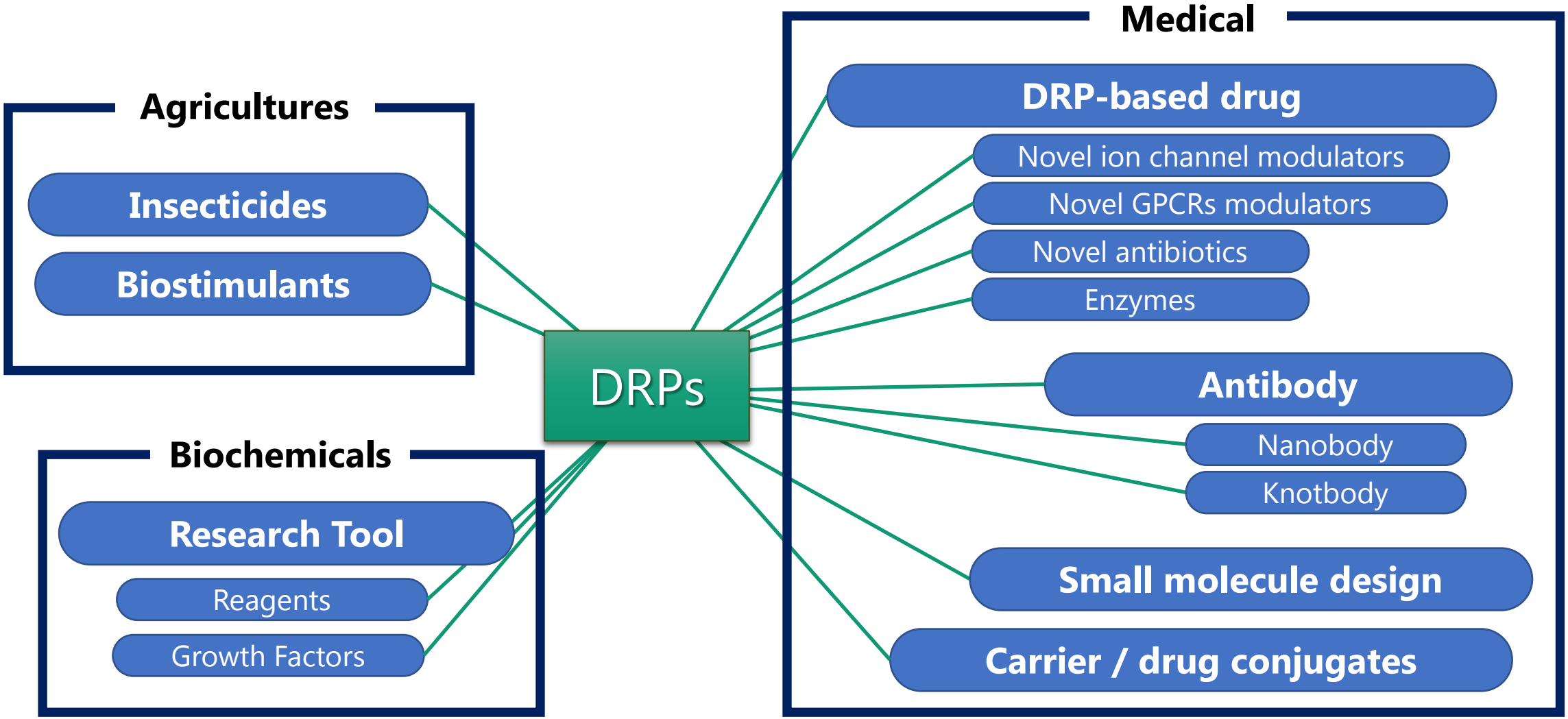
Versatile application of DRPs by Veneno Suite™



Veneno Suite™

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Seeking

- **Business partners (drug discovery and exploration business, joint development, etc.)**
- **Fundraising (seed round under consideration)**

Veneno Technologies Co. Ltd.

2-5-1 Azuma Tsukuba, Ibaraki, Japan

info@veneno.co.jp

https://veneno.co.jp

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Thank you for your attention!