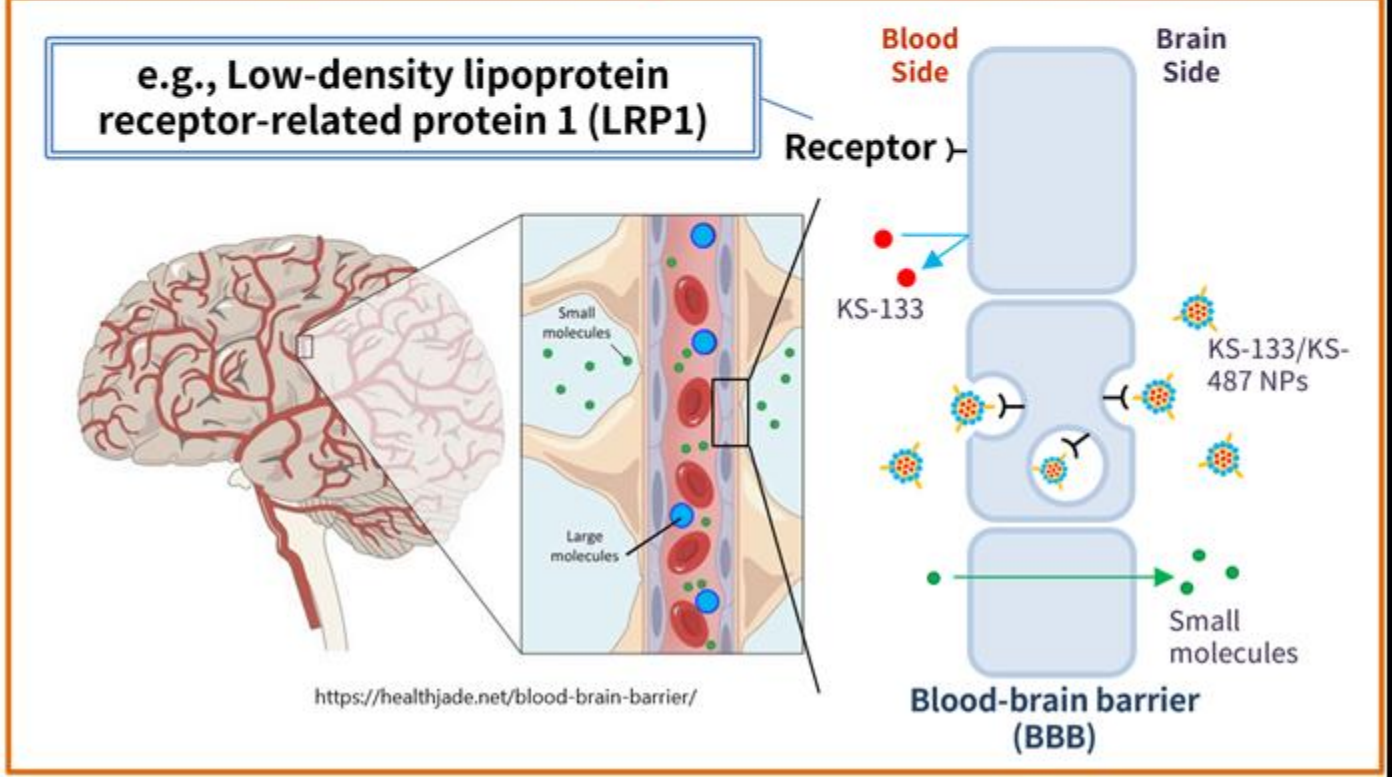
ペプチド

統合失調症の認知機能障害、陰性症状を克服する新規ペプチドナノ製剤の開発

世界初VIPR2拮抗薬で統合失調症を克服する



広島大学　吾郷 由希夫

B-172

Development of peptide-functionalized brain-targeted nanoparticles for treating cognitive dysfunction and negative symptoms in schizophrenia

統合失調症認知機能障害、陰性症状を克服する脳移行性新規ペプチドナノ製剤の開発

Department of Cellular and Molecular Pharmacology,
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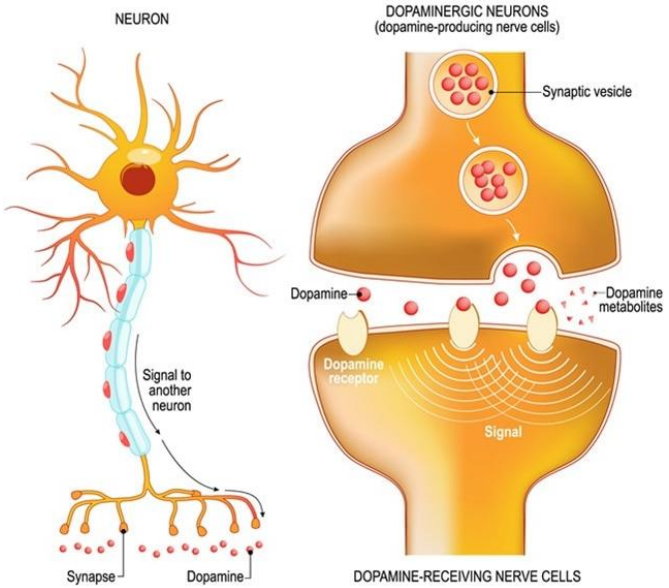
Professor Yukio Ago Ph.D.

教授　吾郷　由希夫

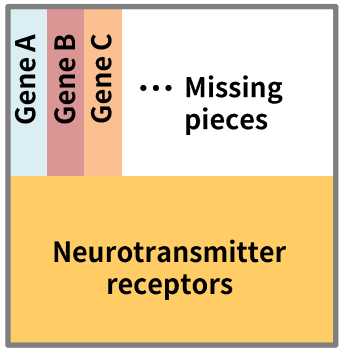
Executive Summary

Aim	To develop a novel drug for treating cognitive dysfunction and negative symptoms in schizophrenia by targeting VIPR2
Stage	Pre-clinical
Lead compound (peptides)	KS-133/KS-487 nanoparticles (NPs)
Indications	● Schizophrenia ● Treatment-resistant schizophrenia
Patient Population	● 24 million people worldwide may be diagnosed with schizophrenia in their lifetime. ● The estimated societal burden of schizophrenia in the US in 2019 was $343.2 billion. ● The market size was valued at USD 21.5 billion.
Mechanism of Action	KS-133: Antagonist of the vasoactive intestinal peptide receptor 2 (VIPR2) (active ingredient) KS-487: Binding to low-density lipoprotein receptor-related protein (LRP1) (brain transport of KS-133)
Therapeutic modality	KS-133: a bicyclic peptide [M.W. 1559 (13 amino acids)] KS-487: a cyclic peptide [phospholopids-conjugated KS-487 = M.W. 3318 (14 amino acids)]
Advantages in Drug Discovery Research	● Currently, no compound is under development as a VIPR2 antagonist, making our product the world's first. ● This formulation may effectively treat negative symptoms and cognitive dysfunction, both of which are unmet medical needs in the treatment of schizophrenia. ● It is a single, non-monoamine target that can be used with existing drugs.
Comparison with competitive products	● Its mechanism of action is completely different from that of existing drugs targeting the monoaminergic system. ● As a medium-sized molecule, it is expected to reduce off-target effects. ● Unlike existing drugs, it does not cause side effects such as weight gain.
Role of this business partner(s)	● Technology collaboration and research on adding sustained functionality or sustained release ● Optional: Technology collaboration and research on acquiring low-molecular-weight compounds (e.g., HTS) ● GLP safety studies and clinical development (e.g., clinical trials, manufacturing, and marketing)

Backgrounds; Unmet needs in the treatment of schizophrenia



https://www.news-medical.net/health/GABA-Activation-and-Dopamine-Suppression.aspx



Development of novel drugs with different MOAs than existing drugs is desired, because schizophrenia is a complex multi-factor disease,

➢ **Schizophrenia is a chronic, severe, and disabling brain disorder that has affected people throughout history.**

《Characteristics and issues of existing drugs》

Existing drugs to schizophrenia are **efficient for positive symptoms mainly** and have **several neurological and metabolic side effects**. They possess **common mechanism of action (MOA)**, blocking to neurotransmitter receptors such as dopamine, serotonin, and adrenaline receptors.

《What is desired》

Approximately **30% of patients show treatment resistance** to existing therapeutic drugs. **Improvement of cognitive dysfunction is important** for patients to reintegrate into society and improve their quality of life, but **none of the drugs for schizophrenia have been approved for efficacy against cognitive dysfunction**.

Treatment-resistant schizophrenia

- **Treatment resistant schizophrenia (TRS)** has been defined as the persistence of symptoms despite ≥2 trials of antipsychotic medications of adequate dose and duration with documented adherence.
- TRS occurs in up to **34% of patients** with schizophrenia.
- TRS patients have greater impairments in verbal learning and memory, processing speed, and executive functioning.

Joober et al., **Schizophr Res** 53: 229-238, 2002
de Bartolomeis et al., **Psychiatry Res** 210: 387-395, 2013
Frydecka et al., **Psychiatry Res** 235: 133-138, 2016

Backgrounds; Activation of VIPR2 signaling confers the risk of schizophrenia

- ✓ Vasoactive intestinal peptide (VIP) receptor 2 (**VIPR2**) gene duplication is associated with schizophrenia with a high odds ratio (14.1)
- ✓ The probability of schizophrenia in people with a VIPR2 mutation is over 90%.

Vacic et al., **Nature** 2011
Sullivan et al., **Nat Rev Genet** 2012
Marshall et al., **Nat Genet** 2017 etc.

nature
International journal of science

Duplications of the neuropeptide receptor gene VIPR2 confer significant risk for schizophrenia

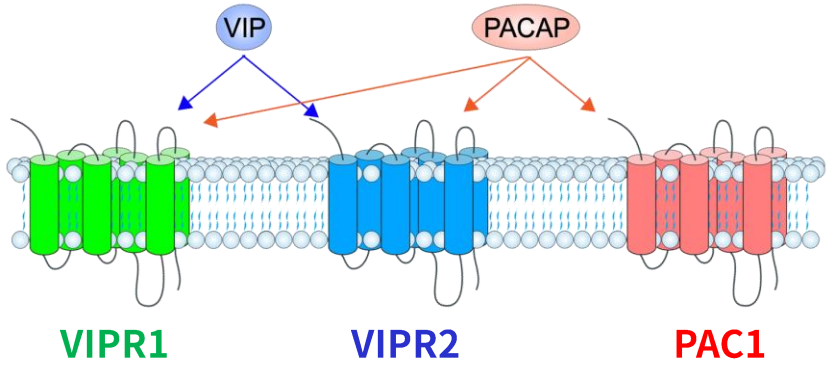
Vladimir Vacic, Shane McCarthy [...] Jonathan Sebat
Nature 471, 499–501 (2011)

Overlapping genes: Several chromosomal changes can lead to either autism or schizophrenia, including, potentially, the newly identified 7q36.3 region.

A neurotransmitter called VIPR2, or vasoactive intestinal peptide receptor, is a candidate gene for schizophrenia and, potentially autism, according to a study published in February in *Nature*.

Several large copy number variations, or CNVs — duplications or deletions of DNA regions — are associated with both schizophrenia and autism, and are believed to contribute to a small, but significant, percentage of people with the disorders.

- ✓ The endogenous ligands of **VIPR2** (also known as VPAC2 receptor) are the neuropeptides **VIP** and **PACAP** (Pituitary adenylate cyclase-activating polypeptide)
- ✓ There are 3 types of PACAP receptors: PAC1, VIPR1 and VIPR2, all of which are class B G protein-coupled receptors (GPCRs).



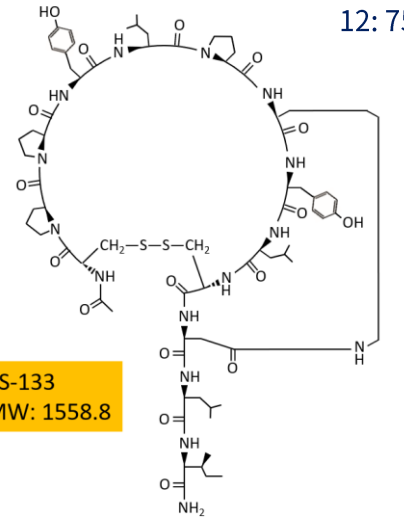
- **Inhibition of synaptic proteins and neurite outgrowth**
- **Abnormalities in neural development and maturation**

Ago et al., **Psychopharmacology** 2015
Takeuchi et al., **Front Neurosci** 2020
Sakamoto et al., **Front Pharmacol** 2021
Ago et al., **Exp Neurol** 2023

Findings by our group:
Overactivation of VIPR2 causes cognitive dysfunction and anhedonia in mice

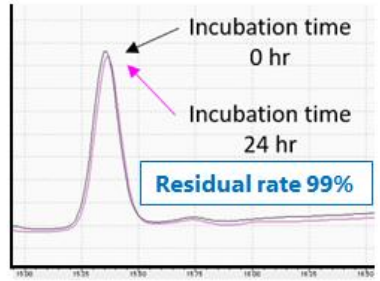
We have developed the selective VIPR2 antagonist peptide, named KS-133

Sakamoto et al., **Front Pharmacol** 12: 751587, 2021



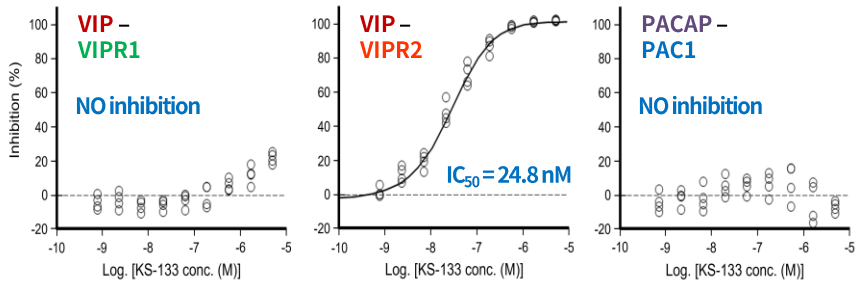
KS-133
MW: 1558.8

Stability in rat plasma



Ac-Cys-Pro-Pro-Tyr-Leu-Pro-Lys-Tyr-Leu-Cys-Asp-Leu-Ile-NH_2

Ca influx assay



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Targeted Goal; Development of a new drug for treating schizophrenia

Our goal

- Development of new therapeutics targeting VIPR2 for schizophrenia
- Development of new therapeutics for treatment-resistant schizophrenia
- Development of therapies aiming to overcome cognitive impairments and/or negative symptoms in schizophrenia
- Development of combination therapies with existing antipsychotics
- Development of personalized therapies for schizophrenia (and/or other psychiatric disorders) with VIPR2 duplication

Aim of (current) research

- **Determining dosage and administration and safety profiles of the lead compound** (KS-133/KS-487 NPs)
- **Developing the companion diagnostic technology** (e.g., electroencephalogram)
- **Elucidating the mechanism underlying the efficacy of VIPR2 inhibition** (Possible relationship between the NMDA glutamate receptor and VIPR2 downstream signaling pathways)
- **Identifying patient populations likely to benefit** (investigation of biomarkers contributing to patient stratification)

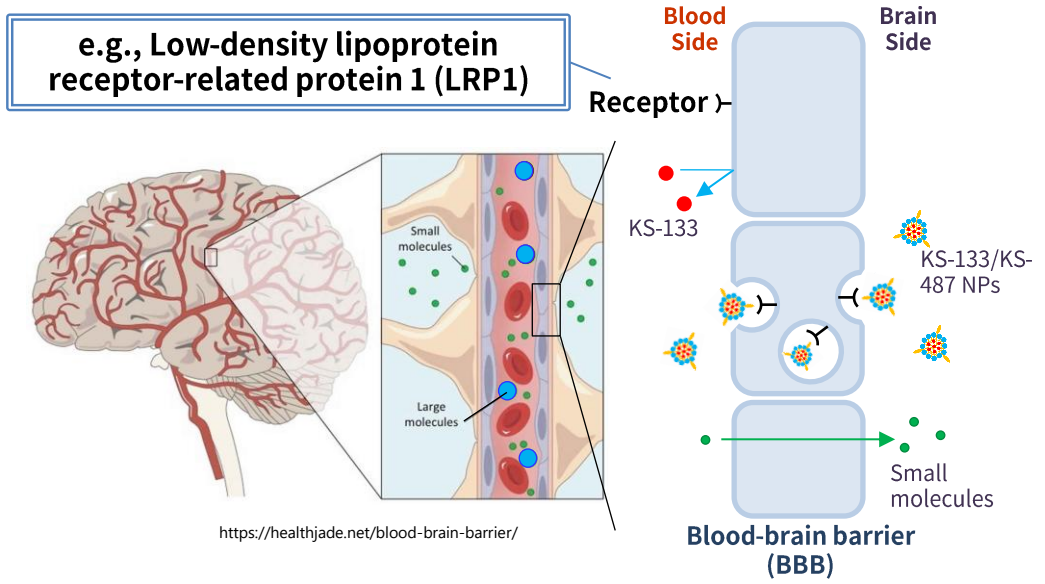
Desired outcome

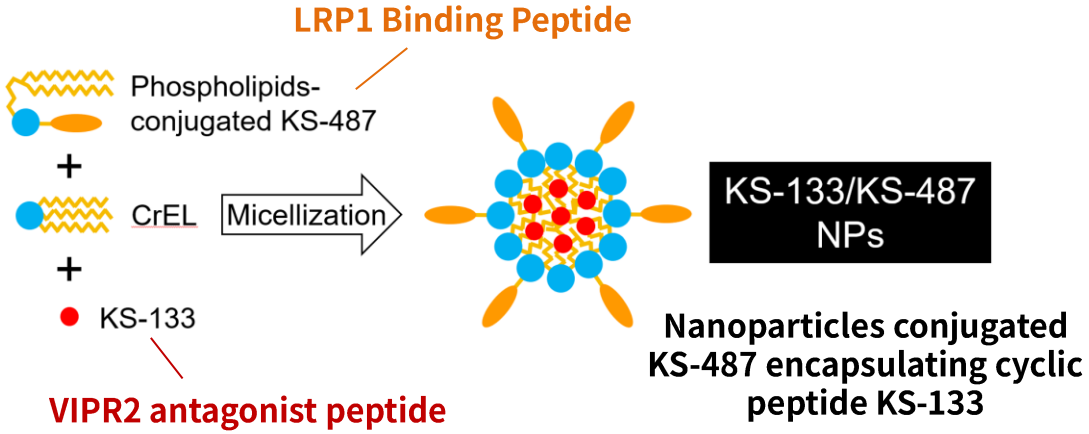
Collaboration with pharmaceutical companies is sought for development support and further advancement of this research.

- **Clinical development** (including clinical trials, manufacturing and marketing)
- Collaborative research into the **development of long-acting injectable or sustained-release antipsychotics**
- Collaborative research on **identifying small molecule drugs that block VIPR2**

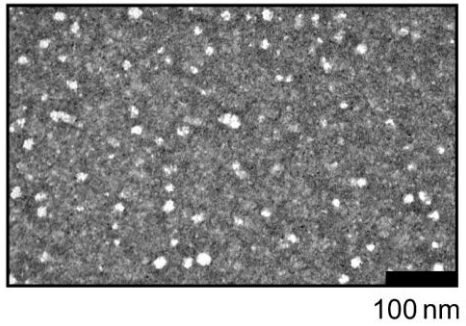
Key Data; LRP1-binding NPs successfully transport KS-133 into the brain

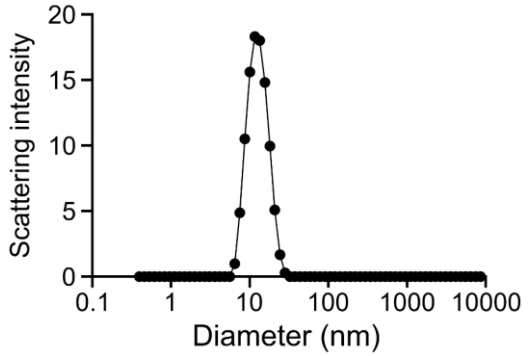
Receptor-mediated transcytosis is an effective way of crossing the BBB





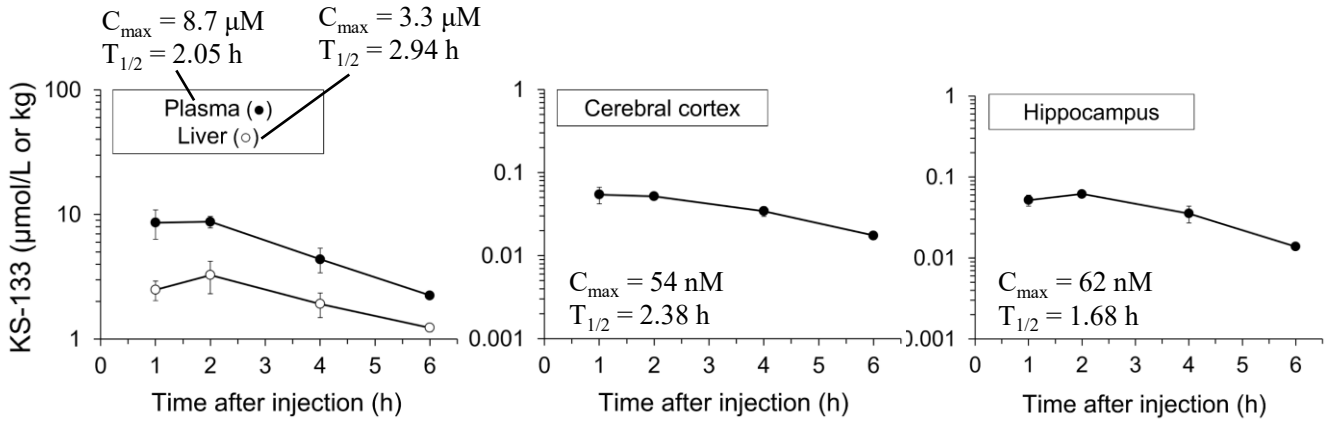
Representative transmission electron microscopy analysis (left) and representative size distribution (right) of KS-133/KS-487 NPs





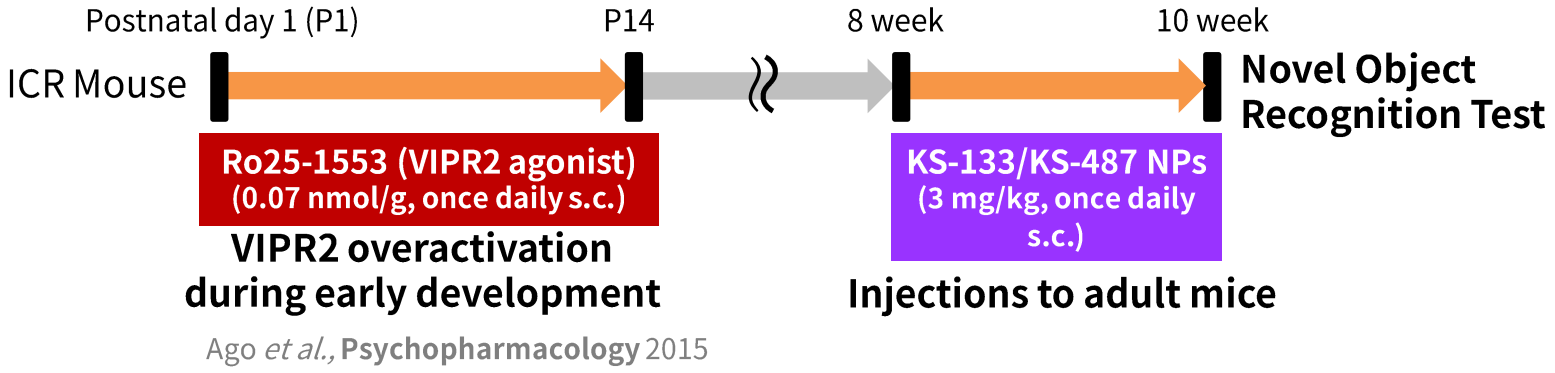
KS-133/KS-487 NPs (size around 13 nm)

KS-133 concentrations in different tissues after single administration of KS-133/KS-487 NPs (3 mg/kg, subcutaneously (s.c.))

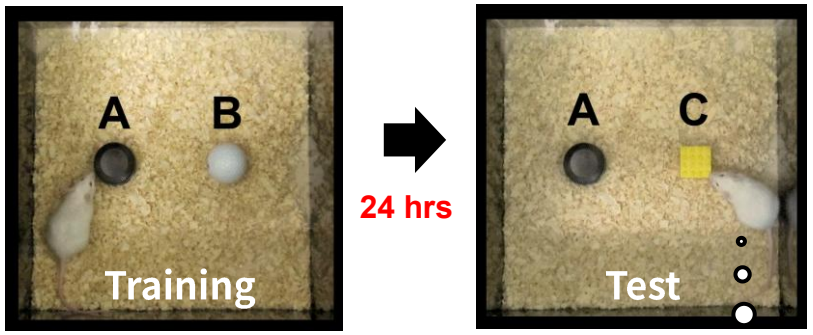


Sakamoto et al., **JACS Au** 4(8): 2811-2817, 2024

Key Data; KS-133/KS-487 NPs restore cognitive function in schizophrenia model



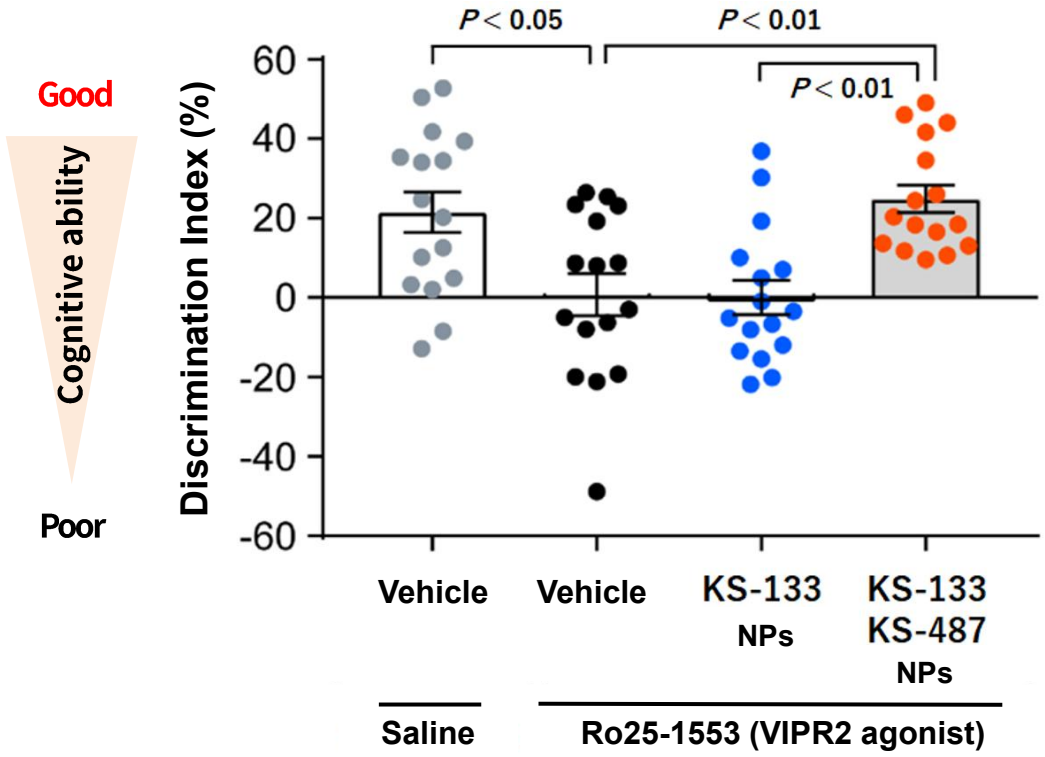
Ago *et al.*, **Psychopharmacology** 2015



Discrimination Index (%) = $\frac{T_C - T_A}{T_C + T_A}$

T_C: Exploration time to **C** in the test
T_A: Exploration time to **A** in the test

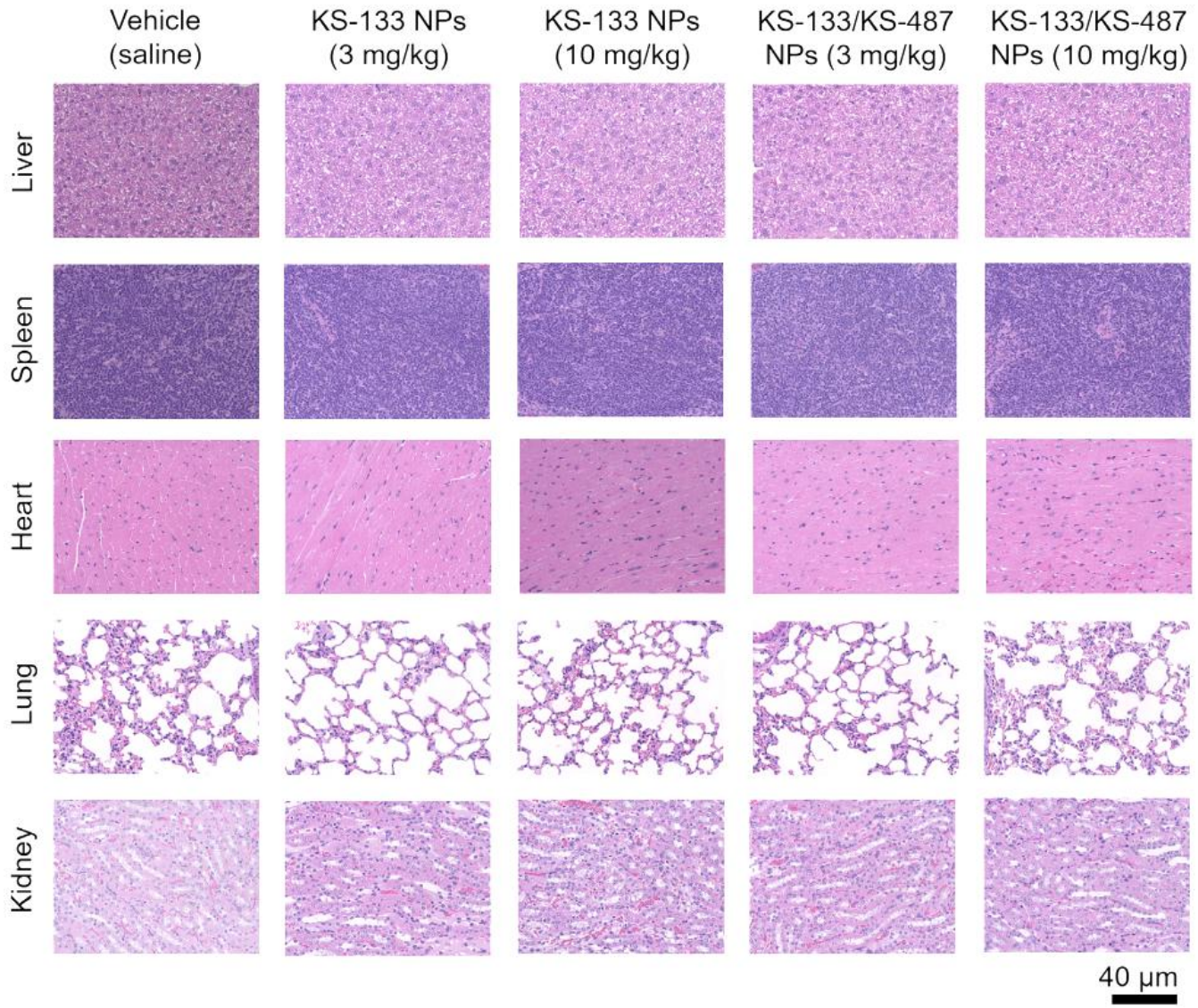
Novel? Familiar?



- **KS-133/KS-487 NPs restore cognitive function to normal levels in mice with a schizophrenia model.**
- **Meanwhile, KS-133 NPs, which do not penetrate the BBB, are ineffective.**
- **KS-133/KS-487 NPs also ameliorate ketamine-induced cognitive impairment and depressive-like behaviors** (data not shown)**.**

Sakamoto et al., **JACS Au** 4(8): 2811-2817, 2024

Key Data; No abnormal findings were found in various organs after the administration of LRP1-targeted KS-133 nanoparticles



Toxicity assessment and histopathological analysis of mice

KS-133/KS-487 nanoparticles administered (s.c., once every 3 days for 19 days, 3 or 10 mg/kg)

Sakamoto et al.,
Advanced Therapeutics 7: 2400278, 2024
https://doi.org/10.1002/adtp.202400278

Advantage; VIPR2 inhibition addresses the unmet medical needs in schizophrenia

- **We developed a bicyclic peptide KS-133, which shows VIPR2 antagonist activity *in vivo* and improves cognitive dysfunction and depressive-like behaviors in a mouse model of schizophrenia.**
- **KS-133 has a different mechanism of action from current therapeutic drugs and exhibits high selectivity for the VIPR2 and potent inhibitory activity against a single-target molecule.**
- **VIPR2 inhibition will be an innovative new drug target that can provide an effective treatment for patients suffering from schizophrenia who show resistance to current medication.**

Subject	Candidate (KS-133)	Existing Medicines
Mechanism of Action	• **VIPR2 antagonist** (New)	• Dopamine D_2/D_3 receptor antagonist • Serotonin $(5\text{-HT})_{2A}$ receptor antagonist • Dopamine D_2/D_3 receptor partial agonist • Muscarinic M1/M4 receptor agonist (Cobenfy™, approved by FDA)
Efficacy	• **Effectiveness for negative symptoms and cognitive dysfunction** • **Addressing treatment-resistant schizophrenia** • Personalized treatment for patients with VIPR2 gene duplication (90% developing schizophrenia)	• Presence of treatment-resistant schizophrenia patients (or even clozapine resistance) • Remaining negative symptoms and cognitive dysfunction
Side effects	• **Expected to reduce off-target effects** because of a mid-size molecular drug • **No weight gain**	• **Extrapyramidal symptoms** • Side effects related to lipid metabolism (e.g., **hyperglycemia**, **weight gain**) due to action on multiple receptors • **Agranulocytosis** (fatal side effect of clozapine)

Summary of "Advantages of this study over competing studies"

- Currently, there are no compounds in development — including discontinued ones — that act as selective VIPR2 antagonists. This makes the applicants' product the world's first of its kind. Its mechanism of action is completely different to that of existing drugs, which target the monoaminergic system.
- We developed a model of cognitive dysfunction in schizophrenia in which first-, second- and third-generation antipsychotics (haloperidol, risperidone and aripiprazole, respectively) were ineffective, but clozapine, a drug used to treat treatment-resistant schizophrenia, was effective. KS-133/KS-487 nanoparticles have also been shown to be effective in this model.
- KS-133/KS-487 nanoparticles may therefore be effective in treating negative symptoms and cognitive dysfunction in schizophrenia, which are currently unmet medical needs.
- It is a medium-sized molecule expected to reduce off-target effects. Unlike existing drugs, it does not cause side effects such as weight gain.

Advantages of Research Results

- We have developed a cell system that stably expresses the drug target molecule, VIPR2. The system is available for compound screening and pharmacological profile analysis.
- Additionally, we have developed mouse models and behavioral tests to assess positive/negative symptoms and cognitive dysfunction in schizophrenia.
- Our modality is a nano-formulation of peptides that can be administered peripherally by combining a drug delivery system.
- The one-year stability of the lead formulation (peptide) has been confirmed.
- Pathological analyses, blood tests, and biochemical tests were performed during the two-week chronic administration of doses up to ten times the effective dose in mice.
- No cardiotoxicity (e.g., QT prolongation) has been confirmed using human iPSC-derived cardiomyocytes.
- Analytical conditions of LC/MS/MS for toxicokinetic (TK) study have been established, and single-dose PK data have been obtained in mice.
- Cross-reactivity in mice, rats, dogs, and humans has been confirmed in vitro.
- A questionnaire survey on the treatment of schizophrenia in Japan has been conducted.

Goal and its Plan for Research and Development

- Development of Novel VIPR2-Targeted Therapies for Schizophrenia
- Development of Novel Therapies for Refractory Schizophrenia
- Development of Therapies to Overcome Cognitive Dysfunction and/or Negative Symptoms in Schizophrenia
- Development of Combination Therapies with Current Antipsychotic Agents
- Development of Personalized Treatments for Schizophrenia (and/or Other Psychiatric Disorders) with VIPR2 duplication

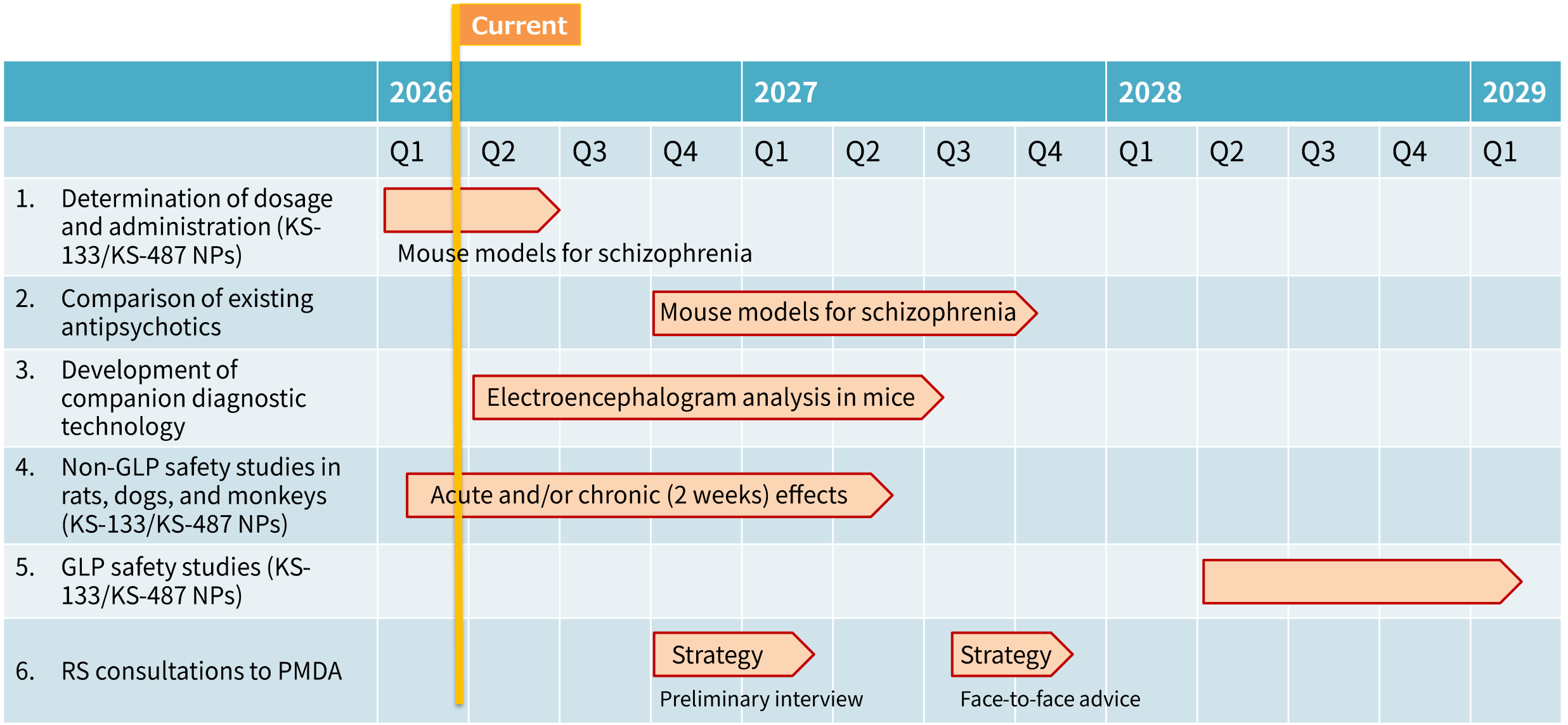
Research plan

- To examine the dose-response effects and identify the minimum effective dose of the lead formulation in animal models (to be completed within FY2026)
- To determine a non-GLP safety study design of the lead formulation (to be completed within FY2026)
- To clarify the mechanism by which VIPR2 inhibition is effective for schizophrenia symptoms

Challenges to achieving the goal

- **Determining dosage and administration and safety profiles of the lead compound** (KS-133/KS-487 NPs)
- **Developing the companion diagnostic technology** (e.g., electroencephalogram)
- **Elucidating the mechanism underlying the efficacy of VIPR2 inhibition** (Possible relationship between the NMDA glutamate receptor and VIPR2 downstream signaling pathways)
- **Identifying patient populations likely to benefit** (investigation of biomarkers contributing to patient stratification)

Time Schedule



Reference （Patents / Key Papers）

Patents

【発明の名称】ＶＩＰＲ２アンタゴニストペプチド
【登録番号】特許第7698318号　【登録日】2025年6月17日
【公開番号】WO/2021/200259　【公開日】2021年10月7日
【出願番号】特願2022-511913　【出願日】2021年3月19日

【発明の名称】癌転移抑制用のＶＩＰＲ２アンタゴニストペプチド
【登録番号】特許第7339471号　【登録日】2023年8月28日
【公開番号】WO/2023/162456　【公開日】2023年8月31日
【出願番号】特願2023-528145　【出願日】2022年12月26日

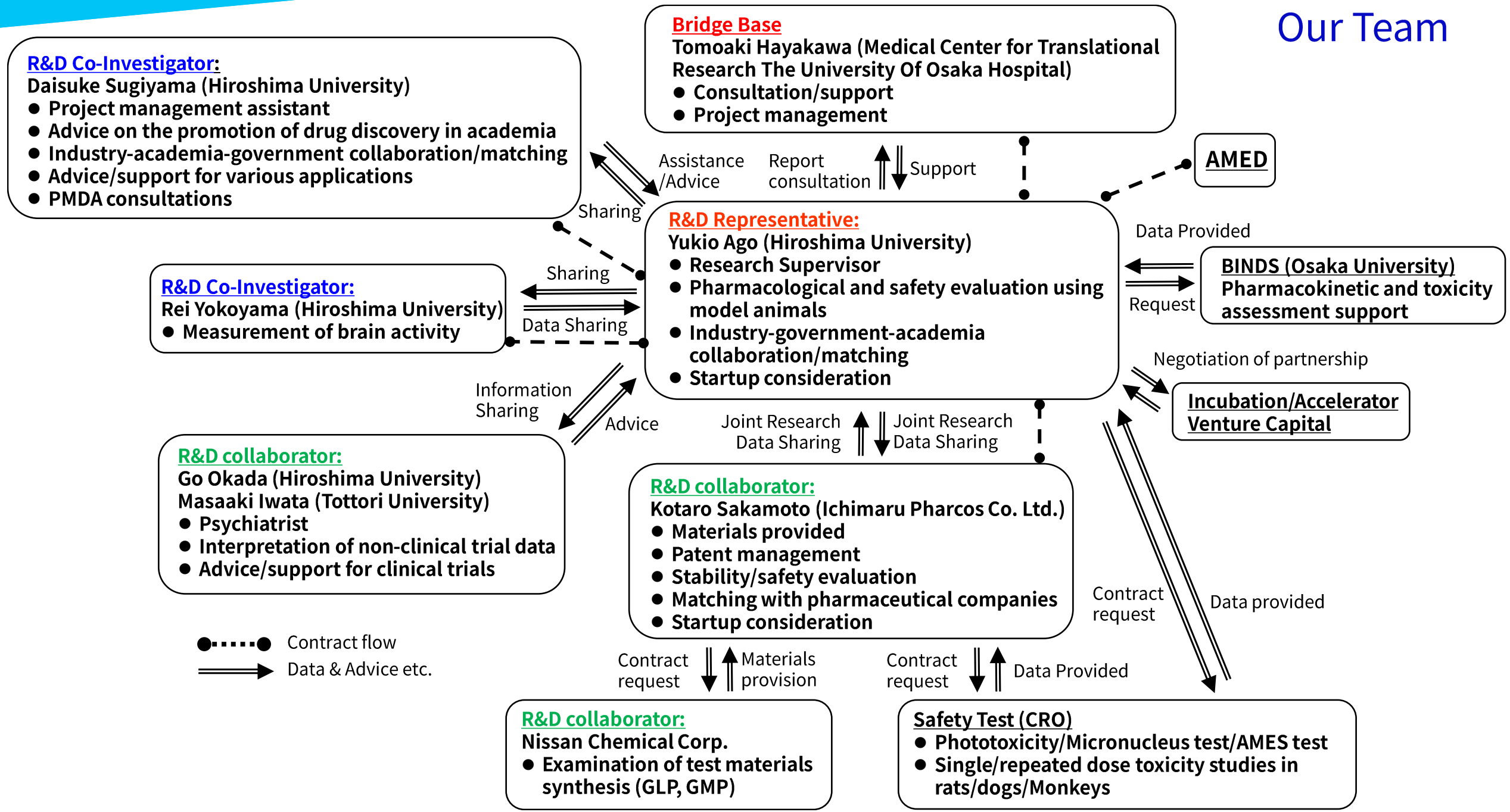
【発明の名称】組成物
【登録番号】特許第7713129号　【登録日】2025年7月15日
【公開番号】WO/2025/142861　【公開日】2025年7月3日
【出願番号】特願2025-520933　【出願日】2024年12月23日

【発明の名称】ＬＲＰ１結合ペプチド
【出願番号】特願2026-018320　【出願日】2026年2月6日

Key papers

1. Ago Y, et al. Reductions in synaptic proteins and selective alteration of prepulse inhibition in male C57BL/6 mice after postnatal administration of a VIP receptor (*VIPR2*) agonist. **Psychpharmacology (Berl)** 232: 2181-2189, 2015.
2. Takeuchi S, et al. Activation of the VPAC2 receptor impairs axon outgrowth and decreases dendritic arborization in mouse cortical neurons by a PKA-dependent mechanism. **Front Neurosci** 14: 521, 2020.
3. Ago Y, et al. Probing the VIPR2 microduplication linkage to schizophrenia in animal and cellular models. **Front Neurosci** 15:717490, 2021.
4. Sakamoto K, et al. Generation of KS-133 as a novel bicyclic peptide with a potent and selective VIPR2 antagonist activity that counteracts cognitive decline in a mouse model of psychiatric disorders. **Front Pharmacol** 12: 751587, 2021.
5. Sakamoto K, et al. AlphaFold version 2.0 elucidates the binding mechanism between VIPR2 and KS-133, and reveals an S-S bond (Cys^{25}-Cys^{192}) formation of functional significance for VIPR2. **Biochem Biophys Res Commun** 636: 10-16, 2022.
6. Asano S, et al. Vasoactive intestinal peptide-VIPR2 signaling regulates tumor cell migration. **Front Oncol** 12: 852358, 2022.
7. Ago Y, et al. Overexpression of VIPR2 in mice results in microencephaly with paradoxical increased white matter volume. **Exp Neurol** 362: 114339, 2023.
8. Asano S, et al. Vasoactive intestinal peptide receptor 2 signaling promotes breast cancer cell proliferation by enhancing the ERK pathway. **Peptides** 161: 170940, 2023.
9. Sakamoto K, et al. Cyclic Peptides KS-133 and KS-487 Multifunctionalized Nanoparticles Enable Efficient Brain Targeting for Treating Schizophrenia. **JACS Au** 4: 2811-2817, 2024.
10. Asano S, et al. Blockade of vasoactive intestinal peptide receptor 2 (VIPR2) signaling suppresses cyclin D1-dependent cell-cycle progression in MCF-7 cells. **J Pharmacol Sci** 154: 139-147, 2024.
11. Asano S, et al. Dimerisation of the VIP receptor VIPR2 is essential to its binding VIP and $G\alpha_i$ proteins, and to its functions in breast cancer cells. **Br J Pharmacol** 182: 3612–3627, 2025.
12. Ono A, et al. Neuron-specific overexpression of human vasoactive intestinal peptide receptor 2 in mice causes cognitive dysfunction and abnormal dendritic morphology in the prefrontal cortex. **J Pharmacol Sci** 160: 111-121, 2026.

Our Team


Bridge Base
Tomoaki Hayakawa (Medical Center for Translational Research The University Of Osaka Hospital)
● Consultation/support
● Project management
R&D Co-Investigator:
Daisuke Sugiyama (Hiroshima University)
● Project management assistant
● Advice on the promotion of drug discovery in academia
● Industry-academia-government collaboration/matching
● Advice/support for various applications
● PMDA consultations
Assistance /Advice
Report consultation
Support
AMED
Sharing
Sharing
R&D Representative:
Yukio Ago (Hiroshima University)
● Research Supervisor
● Pharmacological and safety evaluation using model animals
● Industry-government-academia collaboration/matching
● Startup consideration
Data Provided
Request
BINDS (Osaka University)
Pharmacokinetic and toxicity assessment support
R&D Co-Investigator:
Rei Yokoyama (Hiroshima University)
● Measurement of brain activity
Data Sharing
Negotiation of partnership
Incubation/Accelerator
Venture Capital
Information Sharing
Advice
Joint Research Data Sharing
Joint Research Data Sharing
R&D collaborator:
Go Okada (Hiroshima University)
Masaaki Iwata (Tottori University)
● Psychiatrist
● Interpretation of non-clinical trial data
● Advice/support for clinical trials
R&D collaborator:
Kotaro Sakamoto (Ichimaru Pharcos Co. Ltd.)
● Materials provided
● Patent management
● Stability/safety evaluation
● Matching with pharmaceutical companies
● Startup consideration
Contract request
Data provided
Contract flow
Data & Advice etc.
Contract request
Materials provision
Contract request
Data Provided
R&D collaborator:
Nissan Chemical Corp.
● Examination of test materials synthesis (GLP, GMP)
Safety Test (CRO)
● Phototoxicity/Micronucleus test/AMES test
● Single/repeated dose toxicity studies in rats/dogs/Monkeys

Proposed Partnership Scheme

Role of Proposer

- Elucidate the mechanism by which VIPR2 inhibition is effective in the pathogenesis of schizophrenia
- Determine the patient population in which efficacy is expected
- Examine biomarkers that contribute to patient stratification

Role of this business partner(s)

- Technology collaboration and research on adding sustained functionality or sustained release
- Optional: Technology collaboration and research on acquiring low-molecular-weight compounds (e.g., HTS).
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- GLP safety studies and clinical development (clinical trials, manufacturing, and marketing)

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Mechanism of Action	KS-133: Antagonist of the vasoactive intestinal peptide receptor 2 (VIPR2) (active ingredient) KS-487: Binding to low-density lipoprotein receptor-related protein (LRP1) (brain transport of KS-133)
Therapeutic modality	KS-133: a bicyclic peptide [M.W. 1559 (13 amino acids)] KS-487: a cyclic peptide [phospholopids-conjugated KS-487 = M.W. 3318 (14 amino acids)]
Advantages in Drug Discovery Research	● Currently, no compound is under development as a VIPR2 antagonist, making our product the world's first. ● This formulation may effectively treat negative symptoms and cognitive dysfunction, both of which are unmet medical needs in the treatment of schizophrenia. ● It is a single, non-monoamine target that can be used with existing drugs.
Comparison with competitive products	● Its mechanism of action is completely different from that of existing drugs targeting the monoaminergic system. ● As a medium-sized molecule, it is expected to reduce off-target effects. ● Unlike existing drugs, it does not cause side effects such as weight gain.
Role of this business partner(s)	● Technology collaboration and research on adding sustained functionality or sustained release ● Optional: Technology collaboration and research on acquiring low-molecular-weight compounds (e.g., HTS) ● GLP safety studies and clinical development (e.g., clinical trials, manufacturing, and marketing)