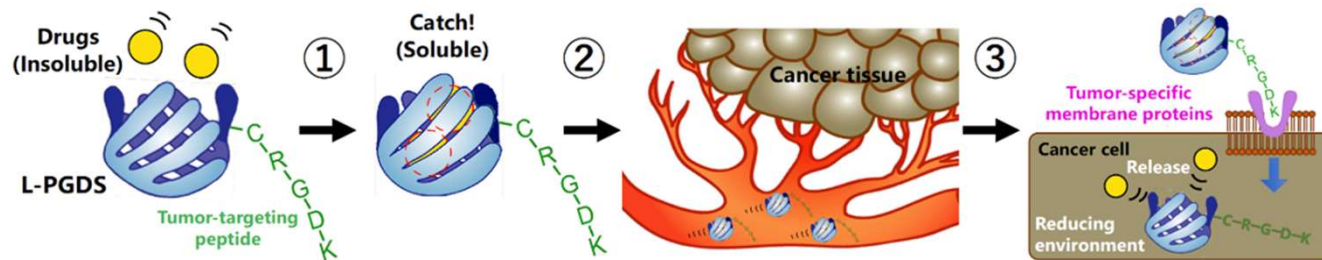


DDS技術応用 医薬品

**難溶性薬剤を放出制御し、
がん細胞に到達させる
革新的DDS基盤のがん治療薬**



創薬科学 乾隆

Development of a Novel Therapeutic for Refractory Cancers Using a Protein-Based DDS with Controlled Drug Release

**薬剤放出制御機能を有するタンパク質DDSにより
難治性がん治療薬の創出を目指す研究**

**Graduate School of Drug Discovery Sciences,
Osaka Metropolitan University**

Takashi Inui, Ph.D. | Professor

大阪公立大学 大学院創薬科学研究科

教授 乾 隆

Executive Summary

Project Goal:

To formulate **Compound A**, a highly potent but poorly water-soluble **mitochondrial Complex III inhibitor**, using an engineered human **L-PGDS-based protein carrier (Pocket Protein DDS: PP-DDS)**, with the goal of developing a novel therapeutic for refractory solid tumors.

Current R&D Stage:

Preclinical Development. In vitro efficacy has been thoroughly validated, and initial in vivo anti-tumor activity and preliminary safety have been confirmed in mouse models.

Mechanism & Modality:

Mechanism of Action: Inhibition of **mitochondrial Complex III and oxidative phosphorylation (OXPHOS)**, leading to disruption of tumor energy metabolism.

Modality: A small-molecule anticancer agent encapsulated in an engineered human protein-based drug delivery carrier (**PP-DDS**).

Target Indications:

OXPHOS-dependent refractory solid tumors including glioblastoma, pancreatic cancer, and small cell lung cancer.

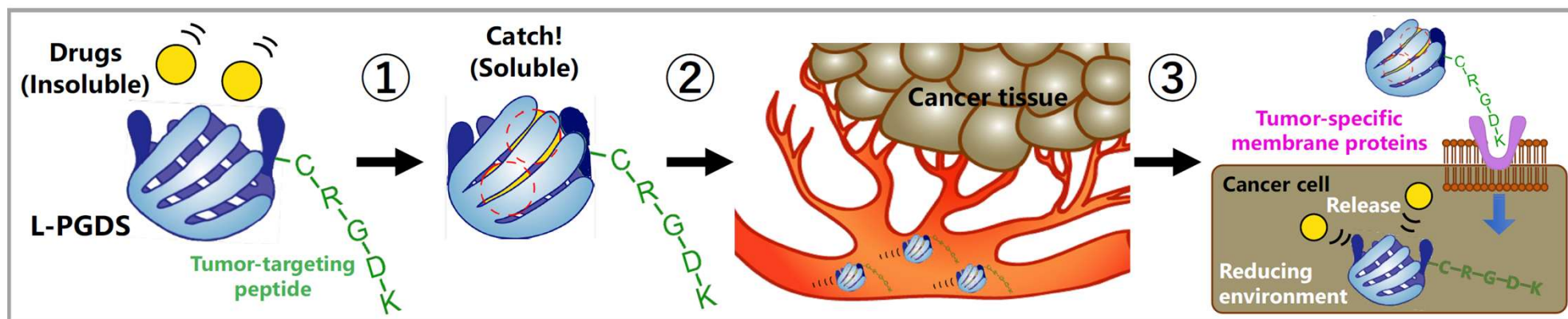
Competitive Advantages:

Unique MOA distinct from standard chemotherapies; controlled drug release in the tumor microenvironment (reducing systemic toxicity); high biocompatibility and low immunogenicity of the human-derived protein carrier; and potentially cost-effective recombinant protein production in *E. coli*.

Partnership Opportunities:

Seeking pharmaceutical partners for co-development post-preclinical POC, licensing out, or CDMO collaborations for manufacturing scale-up.

Backgrounds: Unmet Medical Needs and the “Valley of Death” in Drug Discovery



Targeted Goal: Unlocking the Potential of Promising but Poorly Water-Soluble Drug Candidates through Proprietary Protein-Based DDS Technology to Address Unmet Medical Needs in Oncology.

Target Market Size (Annual Incidence):

Small Cell Lung Cancer (SCLC): ~270,000 new cases globally (~13,000–20,000 in Japan).

Pancreatic Cancer: ~510,000 new cases globally (~48,000 in Japan).

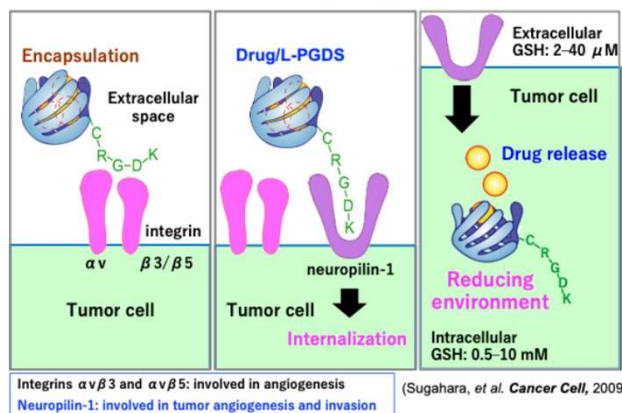
Glioblastoma (GBM): ~180,000–200,000 new cases globally (~2,500–3,000 in Japan).

Development & Exit Strategy: Complete the preclinical POC package, establish a clear regulatory pathway through PMDA RS Strategy Consultations, and secure a strategic partner for subsequent clinical development and commercialization.

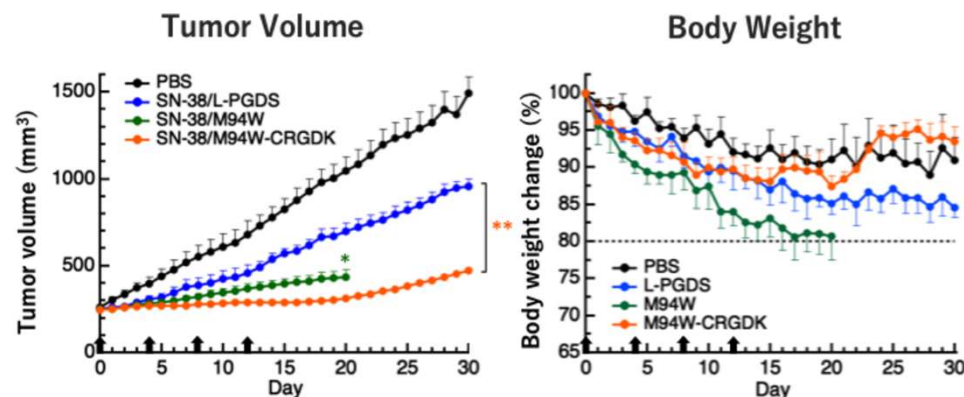
Key Data

L-PGDS Integrates Drug Solubilization, Tumor Targeting, and Controlled Release to Enhance Antitumor Efficacy

Tumor Cell-Targeting DDS



This figure shows the concept of our tumor-targeting DDS. The tumor-targeting peptide CRGDK was introduced into L-PGDS. CRGDK recognizes integrins $\alpha v \beta 3$ and $\alpha v \beta 5$ and subsequently interacts with neuropilin-1, promoting internalization into tumor cells. Once the complex is internalized into tumor cells, it is exposed to a highly reducing intracellular environment. The high intracellular GSH concentration cleaves the disulfide bond in L-PGDS, which induces a structural change and triggers drug release.



Mean $\pm$ S.E. (n = 5); *P < 0.01 vs. SN-38/L-PGDS, **P < 0.001 vs. SN-38/L-PGDS (one-way ANOVA followed by Tukey-Kramer HSD test)

Each SN-38/L-PGDS formulation was administered to prostate cancer model mice by tail vein injection every 4 days for a total of four injections. Both L-PGDS mutant groups (green and orange) showed marked inhibition of tumor growth from the early stage of treatment. Notably, tumor growth remained strongly suppressed even after day 12, when the final dose was administered.

Compound A

Molecular Weight: 427.548, Mitochondria Complex III inhibitor

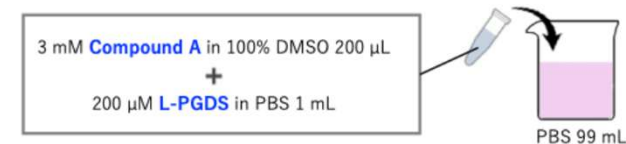
Tumor Cell Line	Antitumor Activity
HTC-116	Human colorectal adenocarcinoma
HT29	Human colorectal adenocarcinoma
Hela	Human cervical cancer
U251	Human glioma
JHH5	Human hepatocellular carcinoma
PC9	Human lung adenocarcinoma

IC₅₀: 0.01–0.1 mM

Further development of Compound A has been limited by its extremely poor aqueous solubility.

Dramatic Improvement in the Solubility of Compound A by L-PGDS

Addition of Compound A in 100% DMSO and L-PGDS solution to PBS



Solubilizing Agent		Compound A Concentration		Ratio
Type	Concentration	$\mu\text{mol/L}$	$\mu\text{g/mL}$	
DMSO	2%	8.40	3.59	1
	10%	414	177	49
β -Cyclodextrin	350 mg/mL	585	250	70
L-PGDS	44 mg/mL (200 μ M)	2359	1008	281

Other Data

Other available non-confidential data

- **L-PGDS** is a human lipocalin protein with a hydrophobic ligand-binding pocket capable of solubilizing a broad range of poorly water-soluble small molecules.
- Published proof-of-concept data are available for **L-PGDS-based** delivery of SN-38 and paclitaxel (PTX).
- Tumor-targeting peptide conjugation can enhance cellular uptake while retaining drug-solubilizing and binding properties.
- Engineered **L-PGDS variants** can improve drug-binding affinity and reduce premature drug leakage.
- **L-PGDS** can be produced recombinantly and has potential as a versatile, designable protein-based DDS platform.

After execution of Non-Disclosure Agreement

- Identity, chemical structure, physicochemical properties, mechanism of action, and potency profile of the proprietary oncology compound (**Compound A**).
- Solubility, binding-affinity, docking, and drug-release data for **Compound A/L-PGDS** and engineered **L-PGDS complexes**.
- In vitro antitumor activity, cancer-cell panel profiling, and selection of responsive tumor models for **Compound A** formulations.
- *In vivo* efficacy for **Compound A/L-PGDS complexes**.
- Optimization strategy, lead **L-PGDS variants**, structural studies, indication strategy, IP plans, and future preclinical/RS development plan.

Reference (Patents / Key Papers)

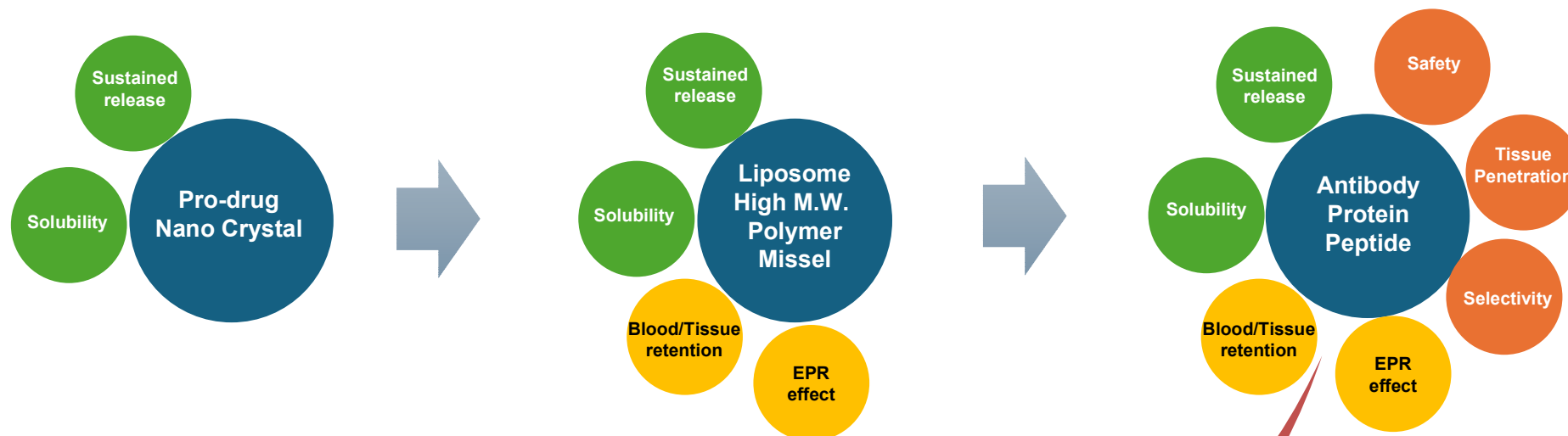
Robust Intellectual Property Portfolio:

- Patent 1 (DDS Core Patent): **WO/2020/235570 (PCT/JP2020/019827)** | Filed: May 19, 2020 | Covers Pharmaceutical Compositions | Filed in: JP, US, EP, CN | Applicant: Osaka Metropolitan, FTO search complete (No infringement risk confirmed).
- Patent 2 (Mutant Substance Patent): **Patent No. 5892648** | Filed: Feb 10, 2012 | Covers L-PGDS mutants and medical uses | JP | Applicant: Osaka Metropolitan Univ.
- Patent 3 (DDS Platform Patent): **Patent No. 5099545** | Filed: Oct 15, 2007 | Covers base drug carrier using *in vivo* proteins | JP | Applicant: Osaka Metropolitan Univ.
- IP Pipeline: New peripheral patent applications covering the optimized "**Compound A-loaded PP-DDS formulation**" are scheduled for filing from October 2027 onwards.

Peer-Reviewed Key Publications:

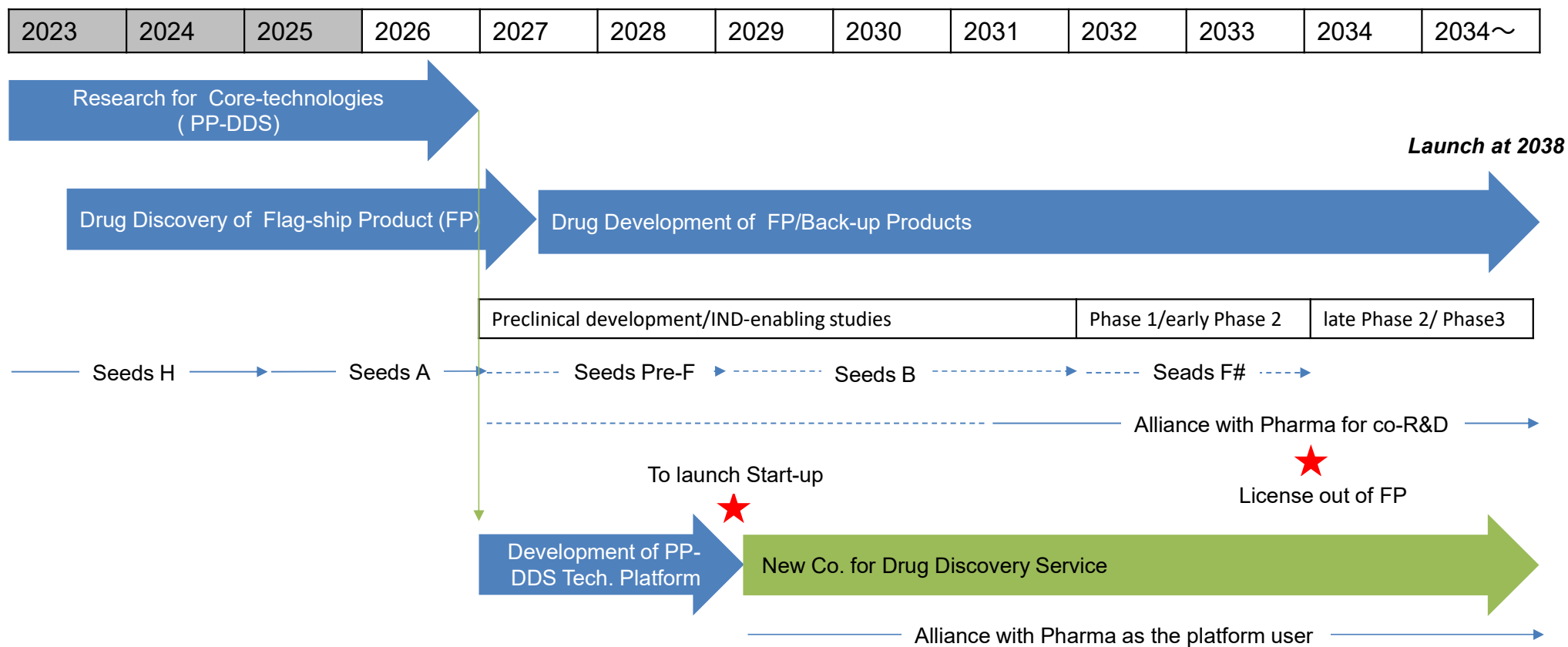
- **ACS Omega**, 11, 3004-3013 (2026): Proven superior therapeutic efficacy ($p < 0.01$) and safety of **L-PGDS-CRGDK-PTX** over free Taxol in breast cancer models.
- **IJBM**, 381, 154313 (2026) : Clarified structural mechanism and dynamic side-chain changes (Trp112, Phe143, Trp54) of **mutant L-PGDS** upon binding drugs.
- **Eur. J. Pharm. Sci.**, 74, 77-85 (2015): Demonstrated **L-PGDS-driven** solubilization mechanisms under pH 7.4 and long-term shelf-stability via lyophilization/spray drying.
- **Biochem. J.**, 443, 75-84 (2012): Established high-yield, low-cost recombinant *E. coli* expression systems for **L-PGDS**.

Competitive Advantage; Highest Versatility for Modern DDS



Evaluation Dimensions	L-PGDS Formulations	Serum Albumin Platform	Antibody-Drug Conjugate (ADC)
Sustained Drug Release	●	◐	○
Blood Retention	◐	●	●
Tissue/Cell Penetration	●	○	◐
Organ/Tissue selectivity	◐	○	◐
Safety	●	●	◐
Manufacturing Cost	●	●	○

Research & Development Load Map



Our Team

Principal Investigator: Takashi Inui, Ph.D. (Professor, Osaka Metropolitan University)

A pioneer in structural biology and protein engineering. Oversees DDS carrier customization, formulation optimization, and *in vitro/in vivo* biological evaluations.



Technology Transfer & BD: Yutaka Ueda and Tadahiro Inoue (Project Appointed Professors, Osaka Metropolitan University)

Experts in R&D strategic planning, intellectual property and business development. Handles licensing negotiations and has established corporate outreach pipelines with global pharma.



Future perspective

Clinical Collaboration: Osaka Metropolitan University Medical School Specialist Team

Integrates direct clinical unmet needs into development, guiding target indication selection, TPP design, and trial protocol drafting.

Candidate of Strategic Corporate Partner: Eisai Co., Ltd.

Provides Compound A under a Material Transfer Agreement (MTA). Conducts regular progress reviews every 4 months, providing invaluable industry-focused guidance, assay protocols, and PK feedback.

A High-Performance Joint Consortium of Academia, Industry, and Clinical Experts

Proposed Partnership Scheme;

Call to Action: Three Pillars of Collaboration

- **Pharma Licensing & Co-Development:**

We are seeking pharmaceutical partners to lead GLP safety studies and subsequent clinical development from IND filing onward, based on our preclinical POC data. While Eisai remains a key partner candidate, we are actively seeking partnerships with global oncology-focused pharmaceutical companies.

- **CDMO Partnership for CMC Scale-Up:**

While laboratory-scale recombinant production in *E. coli* is well established, GMP-compliant scale-up will be required for clinical development. We seek collaboration with CDMOs for technology transfer, process development, and manufacturing feasibility assessment.

- **Strategic Advisory & Clinical Trial Funding:**

To advance PMDA RS Strategy Consultations, outsourced GLP safety studies, and subsequent clinical development, establishing a startup may also be considered as one development option. We welcome partnerships with corporate ventures, specialized CROs, and investors to support development strategy and fundraising.