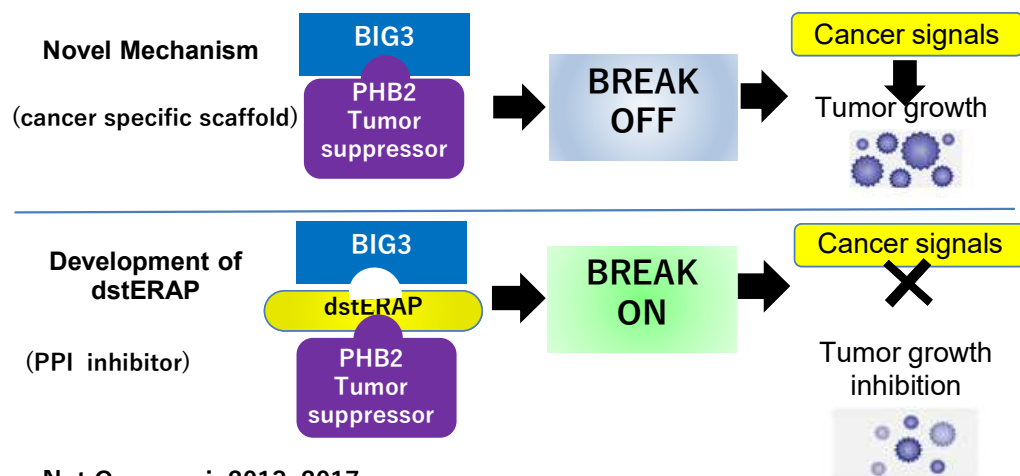


新規作用機序の がん抑制因子活性化ペプチドで 治療抵抗性乳がんを治療

Development of novel therapeutic strategies



Nat Communi. 2013, 2017,
Sci Rep. 2017, IJO 2021



医薬基盤研究所 片桐豊雅

First in human Phase I study of a Tumor Suppressor- Activating Therapeutic Peptide

がん抑制因子活性化ペプチド創薬を目指した第一相臨床試験

National Institutes of Biomedical Innovation, Health and Nutrition (NIBN)
Institute of Biomedical Innovation

Director / Toyomasa Katagiri, Ph.D. | 所長・片桐 豊雅

Executive Summary

UNMET NEED

Acquired treatment resistance and long-term treatment-related toxicities remain major challenges in recurrent or advanced breast cancer.

**MODALITY /
MOA**

The double-stapled peptide dstERAP disrupts the BIG3-PHB2 interaction and reactivates the tumor suppressor PHB2.

CURRENT STATUS

GMP manufacturing and the non-clinical safety package have been completed; an investigator-initiated Phase I trial is planned.

TARGET

Treatment-resistant recurrent or advanced breast cancer; preclinical activity has been demonstrated across ER+, HER2+, and TNBC models.

DIFFERENTIATION

Cancer-specific scaffold protein BIG3; tumor-suppressor reactivation with multi-pathway control; rapid renal clearance with durable antitumor activity.

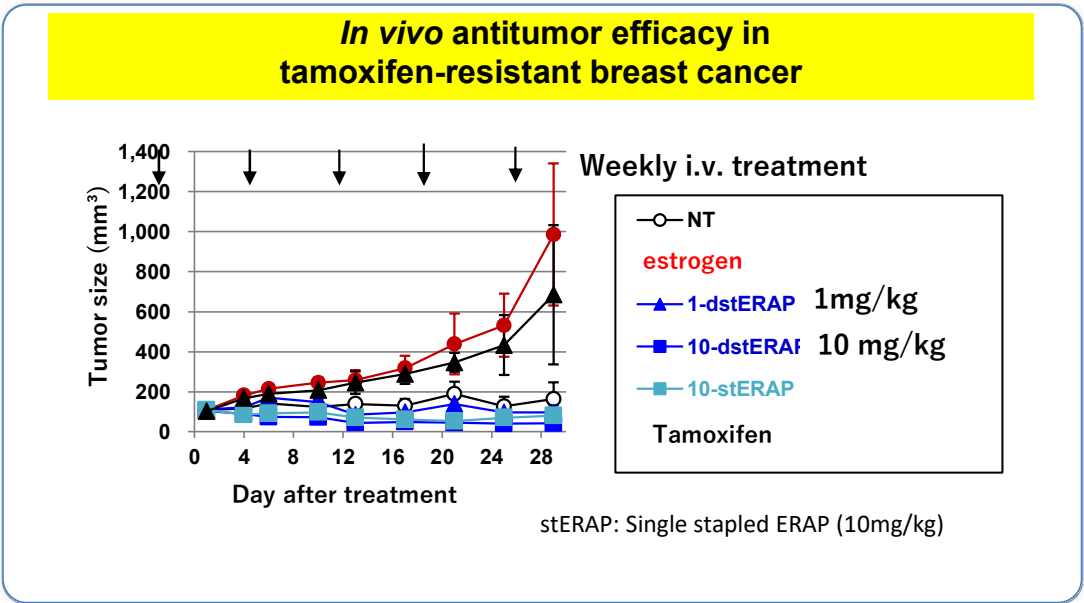
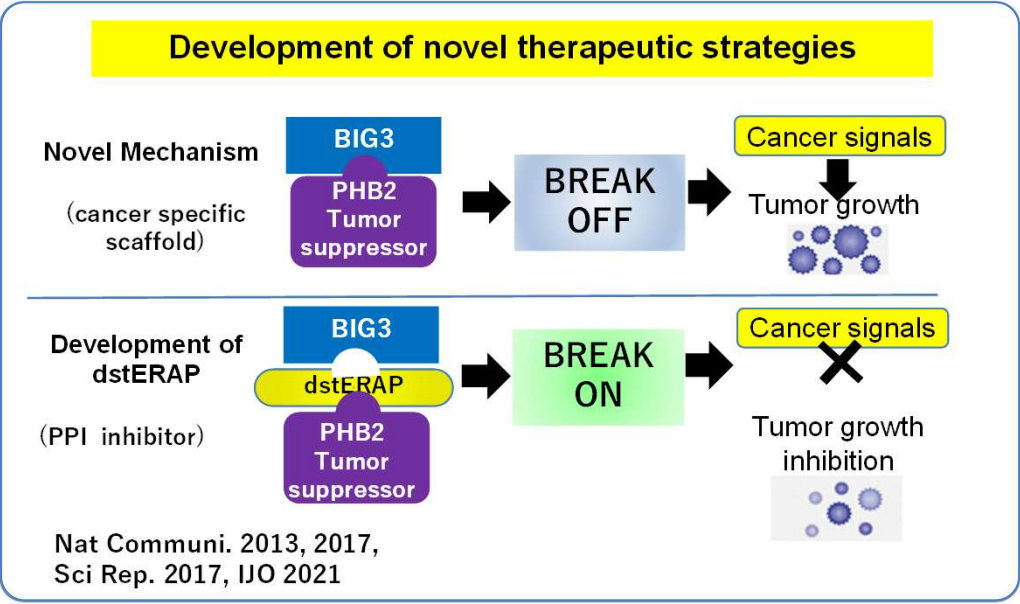
PARTNERSHIP

Seeking pharmaceutical/biotech partners for clinical development, global regulatory strategy, manufacturing optimization, and licensing.

C-70 Backgrounds & Targeted Goal

Unmet Medical Need

- ✓ Acquired or de novo resistance continues to limit durable disease control despite multiple effective drug classes.
- ✓ Long-term endocrine and molecular-targeted therapies are associated with clinically relevant toxicities and treatment burden.
- ✓ New therapies that can overcome diverse resistance mechanisms while minimizing systemic exposure are needed.



Targeted Goal

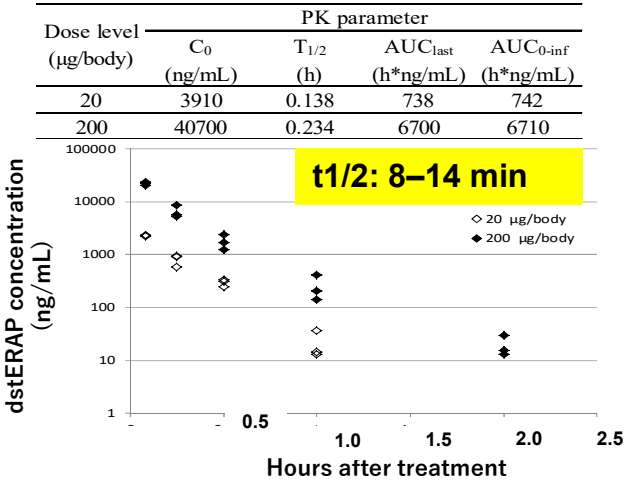
Establish the clinical proof of concept for dstERAP as a first-in-class tumor suppressor-activating therapy for treatment-resistant recurrent or advanced breast cancer, enabling Phase II development and industry partnering.

Key Data — Strong efficacy with short systemic exposure

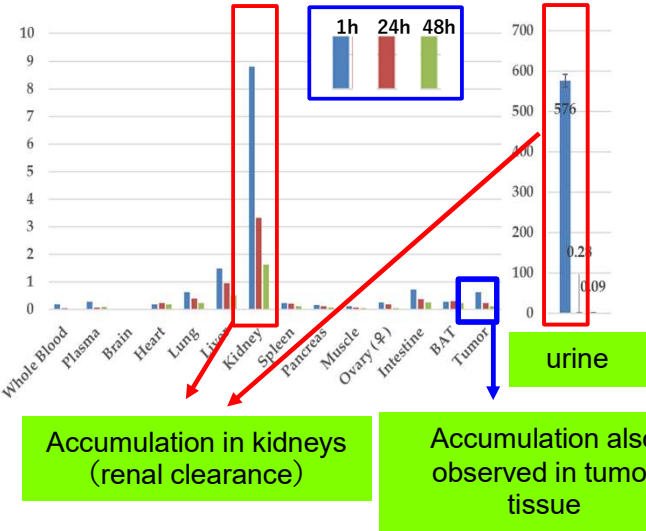
Confirmed POC in vivo model including short retention and long lasting efficacy

Mouse PK: $t_{1/2}$ 8–14 min
Rapid renal clearance with tumor delivery
Antitumor activity maintained for ≥ 7 weeks after a single IV dose in resistant breast cancer model

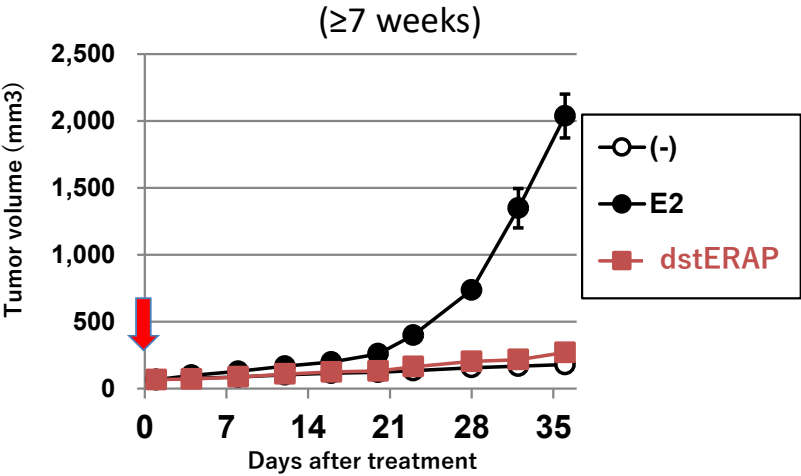
PK Study of dstERAP in Nude Mice (single intravenous injection)



^{64}Cu -dstERAP (^{64}Cu -mAsC)



Anti-tumor effect of dstERAP by a single dose (10 mg/kg i.v.) in Xenograft ER positive breast cancer model

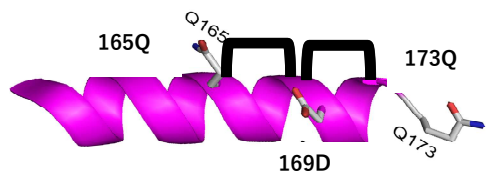


Other Data

Other available non-confidential data

- BIG3 expression / prognostic association and therapeutic-target rationale
- Molecular mechanism of BIG3-mediated PHB2 suppression
- Design and stabilization of double-stapled ERAP (dstERAP)
- BIG3 expression / prognostic association and therapeutic-target rationale
- In vivo efficacy across ER+, HER2+ and TNBC models
- Activity in tamoxifen- and trastuzumab-resistant models
- GLP safety data
- Status of GMP manufacturing for API and clinical material

Double Stapled ERAP (dstERAP)



- Residues (Q165, D169, Q173) in the N-terminal α -helix of BIG3 are critical for binding to PHB2
- Maintains a stabilized α -helical structure
- Resistant to protease degradation
- Capable of penetrating the cell membrane even without a polyarginine

After execution of Non-Disclosure Agreement

- Detailed CMC information
- Full GLP toxicology data
- Detailed PK data
- Additional dose-response and combination studies
- Protocol of clinical trial
- Regulatory consultation materials
- IP information
- Partnering & business proposal



Monitoring every 30 min for 42 h post-dos



Monitoring every 30 min for 49.5 h post-dos

Reference — Patents / Key Papers

Patents

- PCT/JP2012/069131 — ERAP1-derived peptide and use thereof. Granted in Japan, Europe and the U.S.
- PCT/JP2017/001187 — Peptide for cancer treatment and pharmaceutical composition. Granted in Japan and the U.S.
- PCT/JP2018/026904 — Peptide derivatives and pharmaceutical compositions. U.S. patent granted; other jurisdictions pursued.

Selected Key Papers

- Yoshimaru T et al. Nat Commun. 2013;4:2443.
- Yoshimaru T et al. Nat Commun. 2017;8:15427.
- Yoshimaru T et al. Sci Rep. 2017;7:1821.
- Yoshimaru T, Nakamura Y, Katagiri T. J Hum Genet. 2021;66:927–935.

Detailed IP / freedom-to-operate and licensing arrangements should be discussed under NDA with the relevant rights holders.

Competitive Advantage — A differentiated tumor-suppressor activation strategy

Novel mechanism

Reactivates endogenous PHB2 by disrupting the cancer-specific BIG3–PHB2 protein–protein interaction.

Multi-pathway control

Activated PHB2 simultaneously suppresses multiple cancer-related pathways rather than a single oncogenic node.

Resistance setting

Preclinical efficacy demonstrated in endocrine therapy– and anti-HER2 therapy–resistant models.

Safety rationale

BIG3 is highly expressed in breast cancer with limited expression in normal tissues; the mechanism does not require estrogen depletion.

PK / PD profile

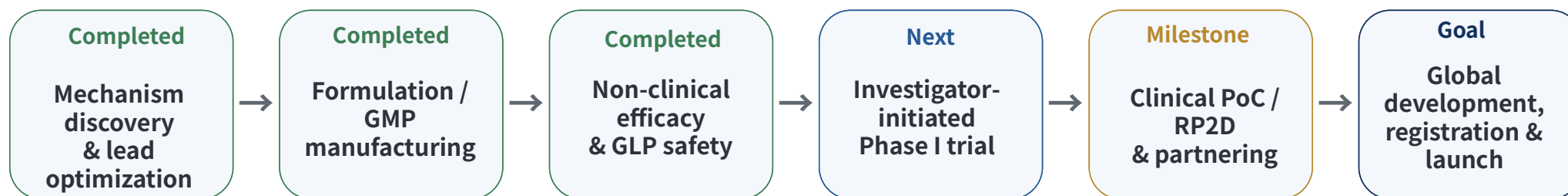
Rapid renal clearance and short systemic exposure, yet durable preclinical antitumor activity.

Combination potential

Potential for combination with established breast cancer therapies based on its distinct mechanism of action.

Positioning: a first-in-class peptide therapeutic designed to overcome treatment resistance through tumor-suppressor reactivation and multi-pathway control.

Research & Development Road Map



Current development focus

- 2026: PMDA consultation, trial setup, IRB review, and clinical-trial notification.
- 2027–2028: Patient enrollment, DLT/PK evaluation, RP2D determination, and clinical proof-of-concept assessment.
- 2028–2029: Prepare Phase II development and pursue partnering/licensing or start-up options.
- In parallel: optimize manufacturing/cost of goods and advance backup small-molecule BIG3–PHB2 inhibitors.

Our Team

NIBN / Katagiri Lab

Discovery biology, mechanism, translational research, biomarker strategy, and overall program leadership.

Clinical / ARO collaborators

Investigator-initiated Phase I trial planning and execution, monitoring, regulatory operations, data management, statistics, and PK analysis.

Manufacturing / CMC partners

GMP peptide manufacturing, formulation, analytical control, and clinical supply.

Industry partner sought

Global clinical development, regulatory strategy, manufacturing scale-up, commercialization, and licensing.

Integrated academic–clinical–industry framework for rapid translation to patients

Proposed Partnership Scheme

What we are seeking

- Pharmaceutical/biotech partner for co-development or licensing
- Clinical development and global regulatory expertise for Phase II and beyond
- CMC scale-up, manufacturing optimization, and cost-of-goods reduction
- Strategic input on indication expansion, combination strategies, and global milestones
- Funding and business-development support for Phase II development, including start-up options where appropriate

Proposed role sharing

NIBN / Academia
Mechanism • Translational data • Biomarkers

Clinical / ARO Network
Phase I execution • Regulatory operations

Industry Partner
Global development • CMC • Registration • Commercialization

Partnering objective: use Phase I safety, PK, RP2D, and preliminary efficacy data to enable Phase II development and accelerate global development of dstERAP for treatment-resistant breast cancer.