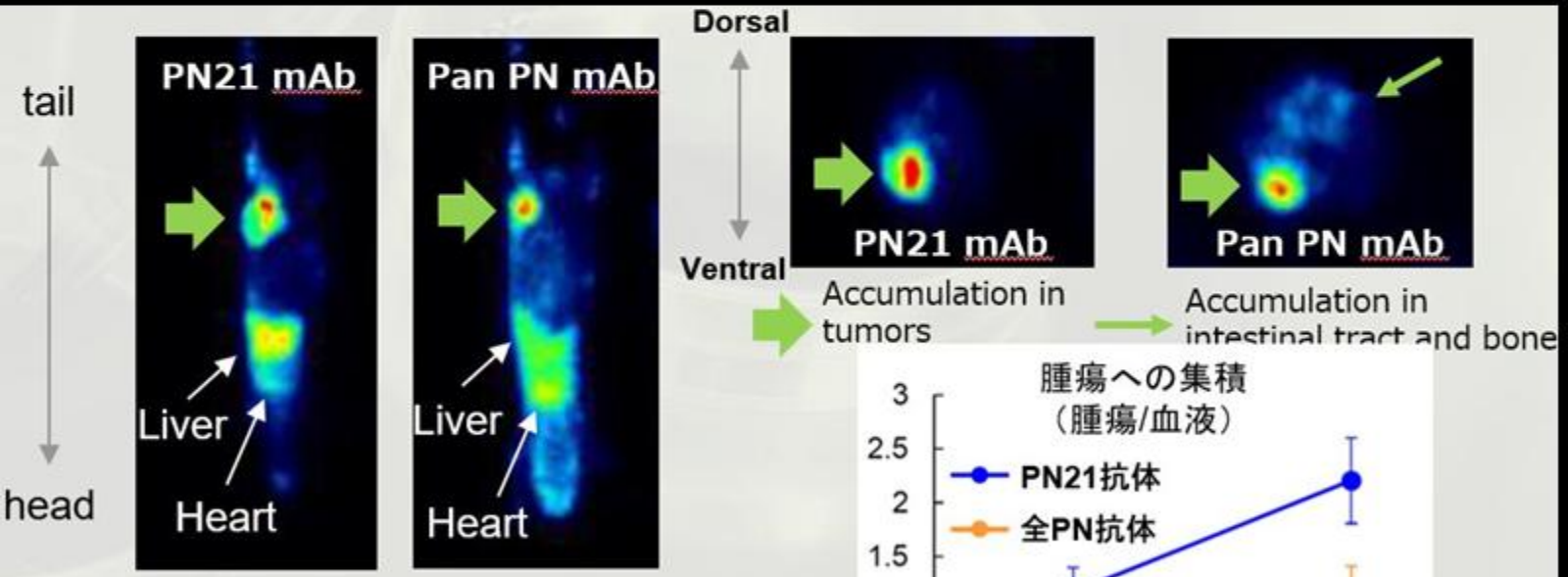
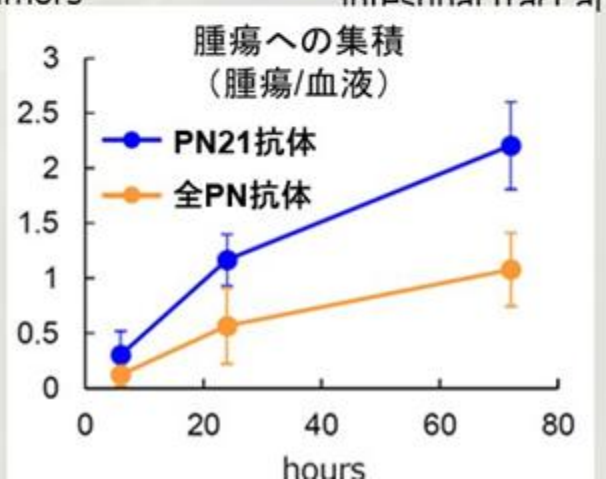
抗体

HER2陰性乳癌転移再発症例への新規治療薬の開発

抗がん剤が生み出す耐性因子を標的に変える





✓ Exon 21 antibodies that do not cross physiological periostin are safe and accumulate in high tumor-specific concentrations

先端分子治療学
谷山　義明

C-061

HER2陰性乳癌転移再発症例への新規治療薬の開発

～病的ペリオスチン抗体による治療薬の開発～

Development of novel therapeutic agents for metastatic and recurrent HER2-negative breast cancer

~Development of therapeutic agents using pathological periostin antibodies~

先端分子治療学
Development of Advanced Molecular Therapy, The University of Osaka

教授・谷山義明
Prof. YOSHIAKI TANIYAMA

Executive Summary of this Proposal

A. Research Assets Held

Research Assets
■ 1. Knowledge regarding therapeutic targets and treatment strategies for specific diseases
■ 2. Candidate substances for the therapeutic targets in item 1 (e.g., neutralizing antibodies, antisense molecules)
■ 3. Various research tools that can be used to validate the therapeutic targets in item 1 or to evaluate the validity of the treatment strategy
(liquid biopsy diagnostic agents, surrogate markers, ISH, CTC, ctDNA, single-cell sequencing)
■ 4. Diagnostic methods / liquid biopsy and ISH that can be used for patient stratification
☐ 5. Foundational technologies that accelerate drug discovery research
(e.g., DDS, drug-modification technologies)
☐ 6. Manufacturing technologies and process technologies related to pharmaceutical production
■ 7. Others (specifically: patents related to periostin

×

B. Forms of Research Collaboration

Forms of Collaboration
•☐ Technical guidance
•■ Transfer of research tools, etc. (MTA)
•■ Joint research
•■ Contract research
•■ Patent licensing
•☐ Establishment of a startup (company)
•■ Fundraising / capital acquisition

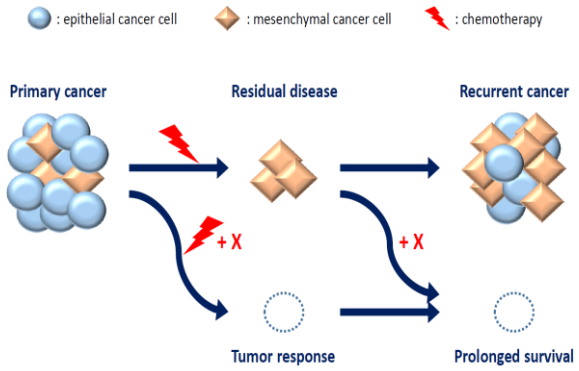
Preferred Forms of Research Collaboration

・Investment in a venture company
•Discussions with potential licensees
•Consideration as an M&A opportunity

Background on drug discovery research projects and drug discovery-related technologies(1)

Chemotherapy-induced "pathological periostin" induces EMT and therapeutic resistance

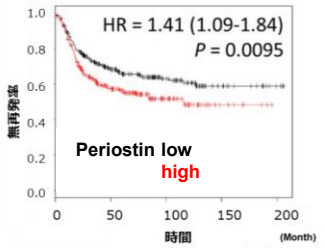
Epithelial-mesenchymal transition (EMT)



EMT modulation (+ X) might prevent RD and prolong patient survival

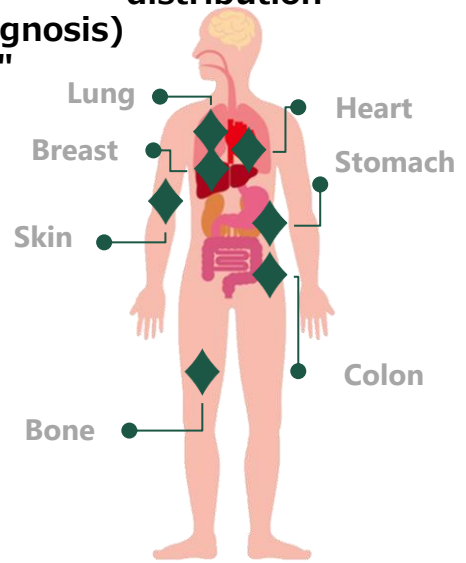
"Correlation with recurrence rate (prognosis) in triple-negative breast cancer"

Relationship between recurrence-free rate of TNBC and periostin expression level

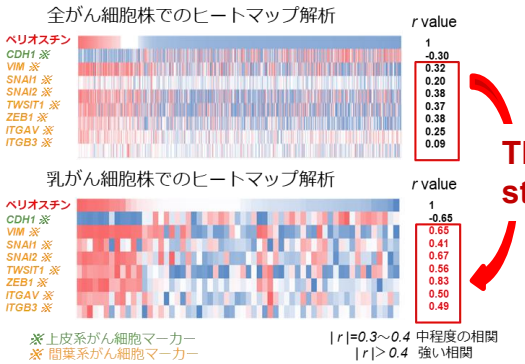


The higher the periostin level, the higher the recurrence rate of triple-negative breast cancer.

Periostin distribution



"Periostin expression correlates with treatment resistance markers in a study using over 1,000 cancer cell lines"

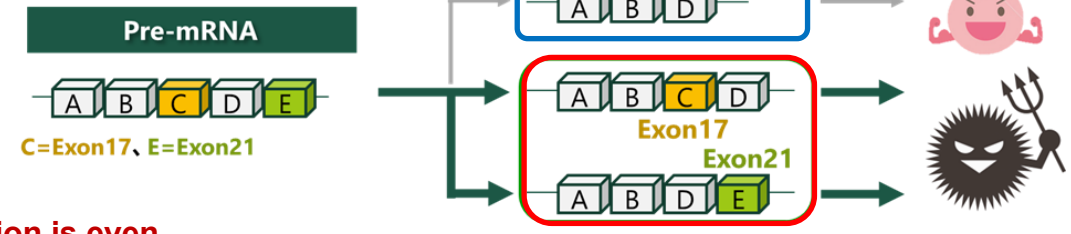


The correlation is even stronger for breast cancer

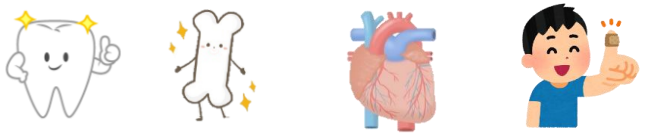
UCSD Prof. Jing Yang collaboration

Taniyama et al. Sci Rep. 2018

Alternative splicing variants of Periostin

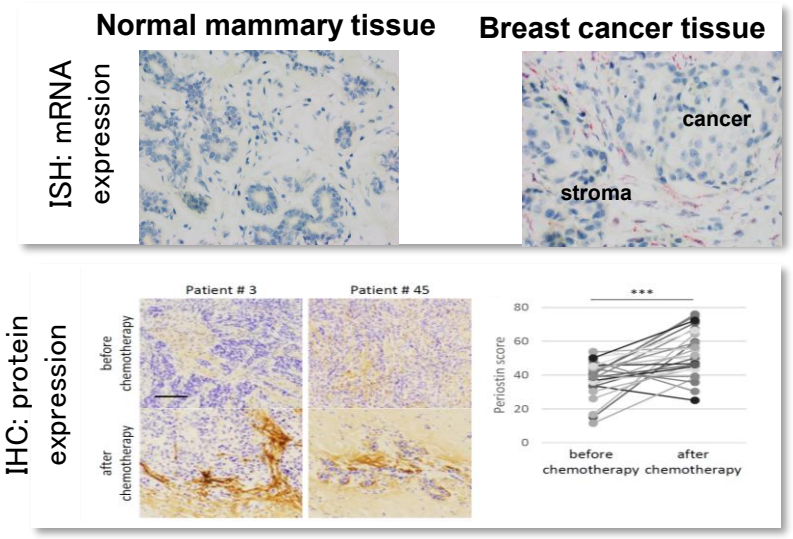


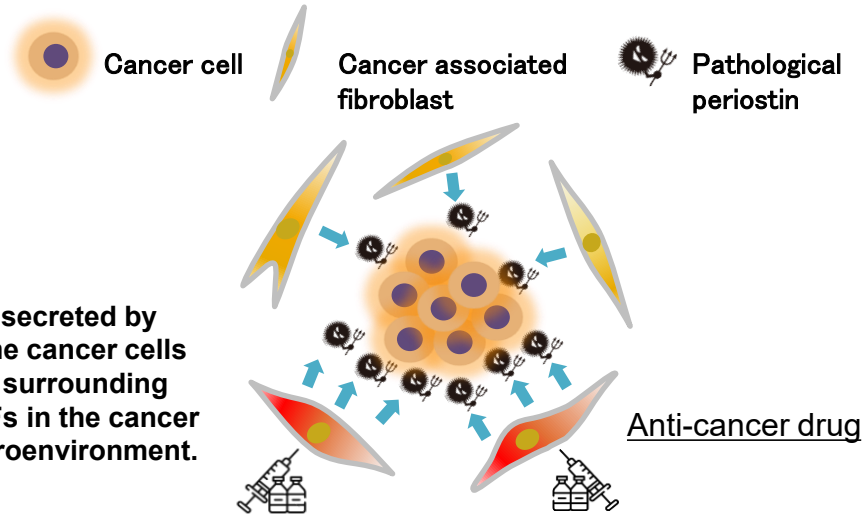
Function of Physiological Periostin



Background to this Drug Discovery Project and/or Biotechnology (2)

Appearance and function of pathological periostin/Pathological periostin is induced by anticancer drug administration and forms treatment-resistant TME

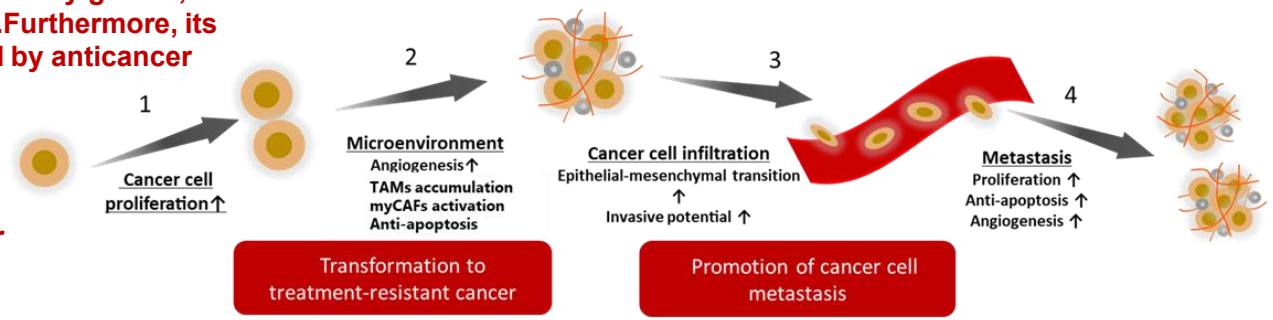




It is secreted by some cancer cells and surrounding CAFs in the cancer microenvironment.

Pathological periostin is secreted almost exclusively in normal mammary glands, but is secreted in breast cancer.Furthermore, its expression is upregulated by anticancer drugs.

Function of Pathological Periostin

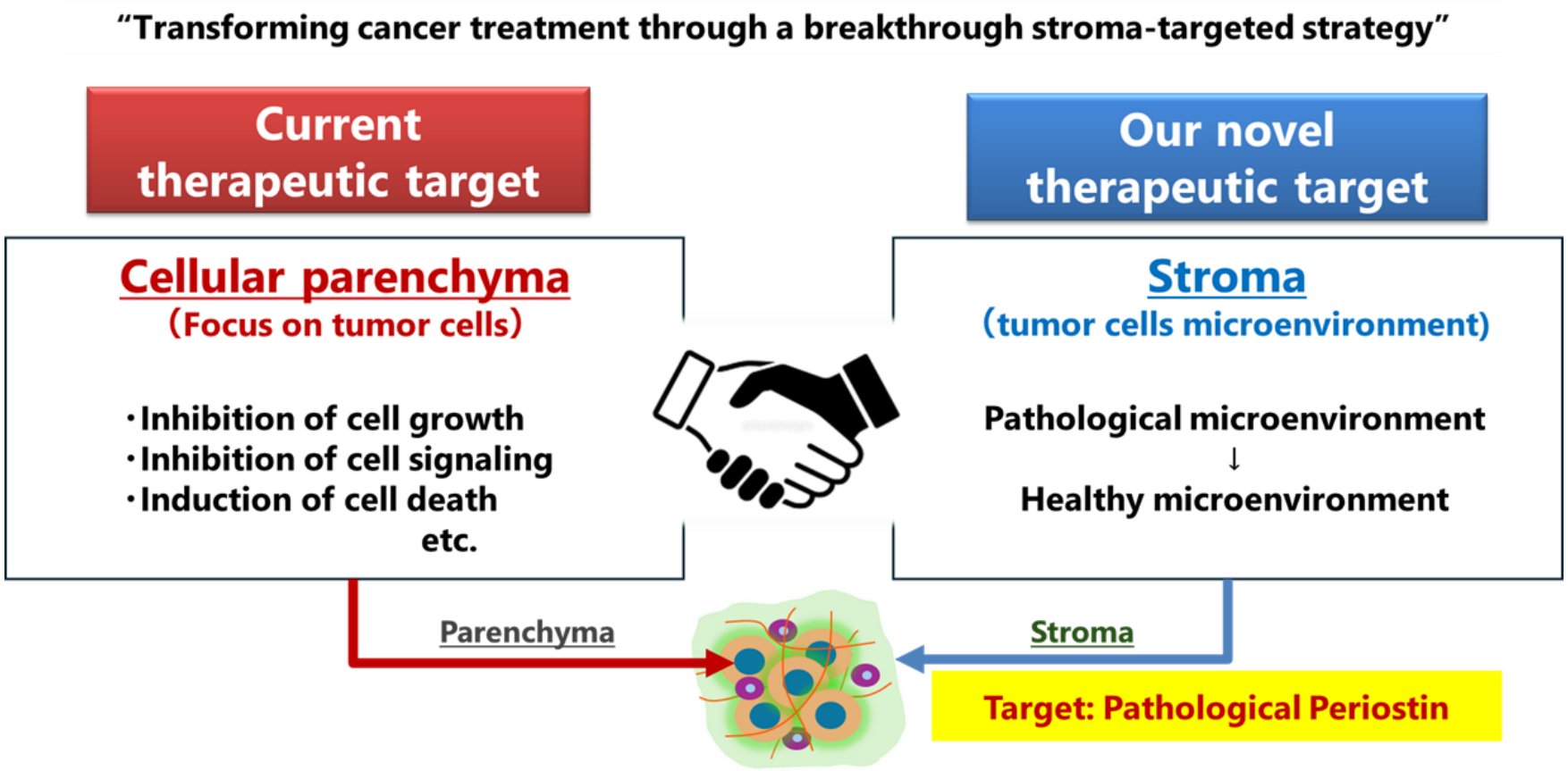


Induce the deterioration of the cancer microenvironment (pathological angiogenesis, TAM induction, CAF activation, anti-apoptotic effects, etc.), leading to cancer growth and metastasis.

Developed a neutralizing antibody that inhibits pathological periostin without inhibiting physiological periostin

Summary of this Drug Discovery Project and/or Biotechnology (1)

A novel therapeutic concept that simultaneously controls cancer cells and stroma

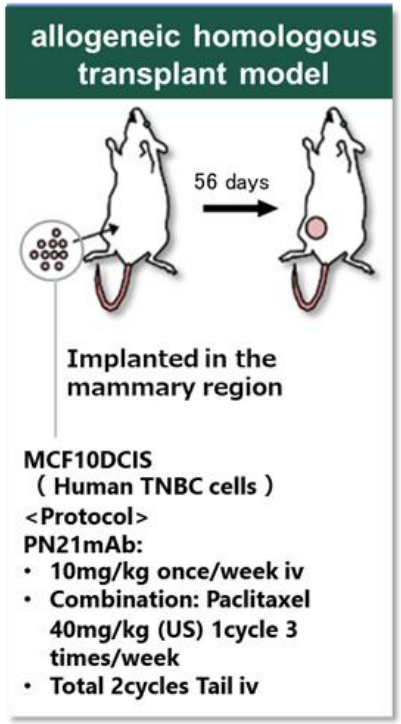


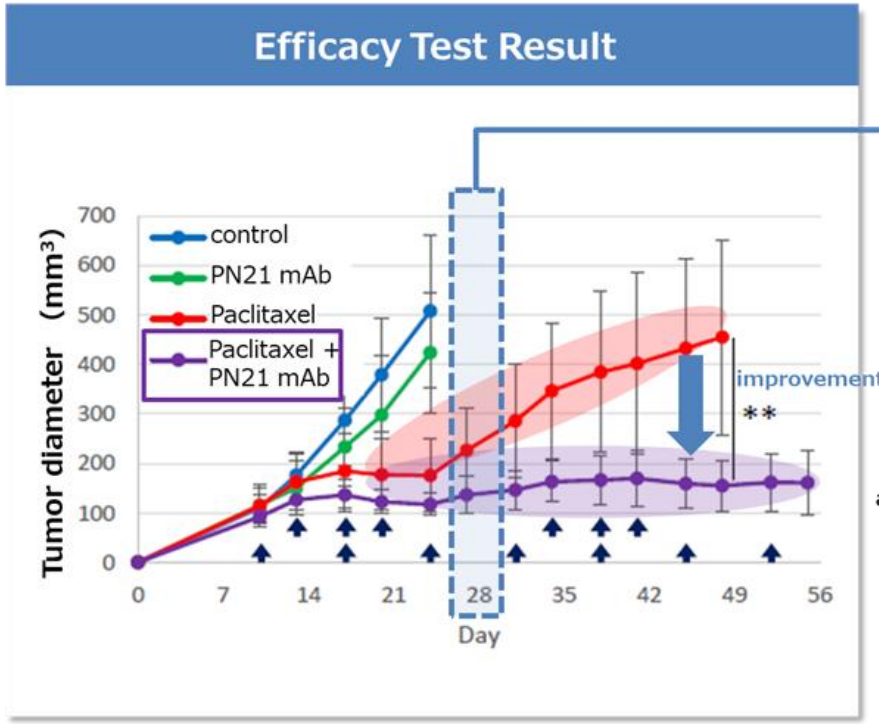
Although treatments that directly attack the cancer parenchyma have been developed, they have not yet shown satisfactory results. Combining these with treatments that attack the stroma will lead to the development of a radical cancer treatment.

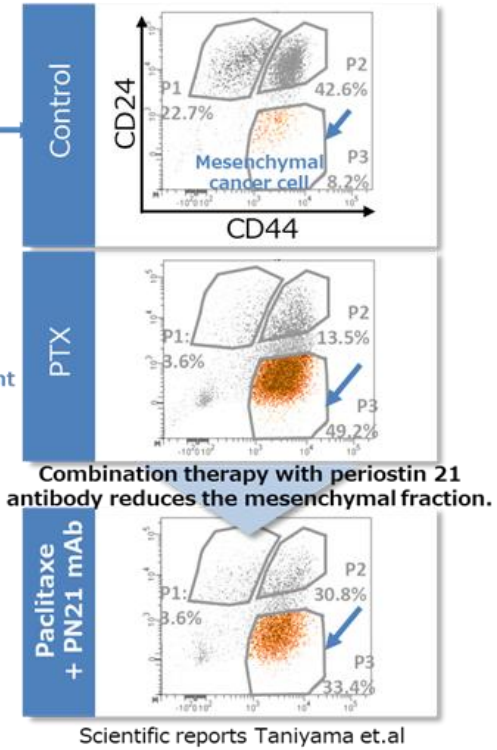
Summary of this Drug Discovery Project and/or Biotechnology (2)

Overcoming chemotherapy resistance in combination with paclitaxel

When chemotherapy (paclitaxel) is administered to TNBC, CD44highCD24low mesenchymal breast cancer cells (breast cancer stem cells) appear, but their appearance is significantly suppressed by the combined use of PN21 antibody, and recurrence is also suppressed.







Combination therapy with periostin 21 antibody reduces the mesenchymal fraction.

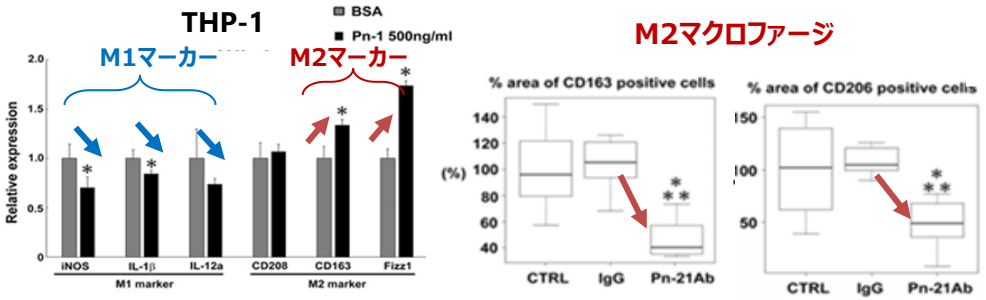
Scientific reports Taniyama et.al

Summary of this Drug Discovery Project and/or Biotechnology (3)

Pathological periostin antibody simultaneously blocks M2 macrophage accumulation, pathological angiogenesis, epithelial-mesenchymal transition, and cancer-associated fibroblast activation

① Suppression of TAM/M2

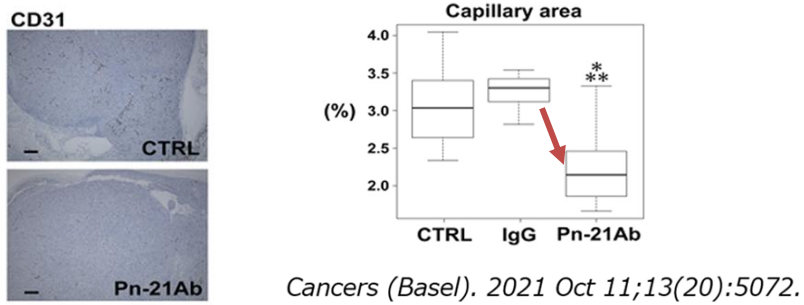
Pathological periostin	・Increased CCL2 levels promote the accumulation of M2 macrophages in the tumor microenvironment ・M1 macrophages decrease ・M2 macrophages increase
Periostin antibody (PT0101)	・M2 macrophages are suppressed



Cancers (Basel). 2021 Oct 11;13(20):5072.

② Inhibition of pathological angiogenesis

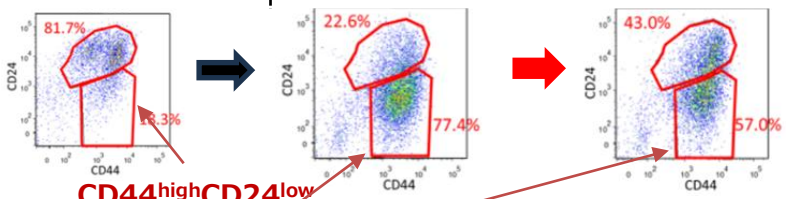
Pathological periostin	・Increases VEGF and induces pathological angiogenesis
Periostin antibody (PT0101)	・Suppression of CD31-positive blood vessels in the cancer microenvironment



Cancers (Basel). 2021 Oct 11;13(20):5072.

③ Inhibition of epithelial-mesenchymal transition in cancer cells

Pathological periostin	Increased by anticancer drugs Increased treatment resistance via survival signaling/Akt Increased expression of Twist and Snail, inducing epithelial breast cancer to mesenchymal (cancer stem cell) stage, increasing treatment resistance
Periostin antibody (PT0101)	Suppression of survival signals - Suppression of the emergence of mesenchymal breast cancer cells in the cancer microenvironment

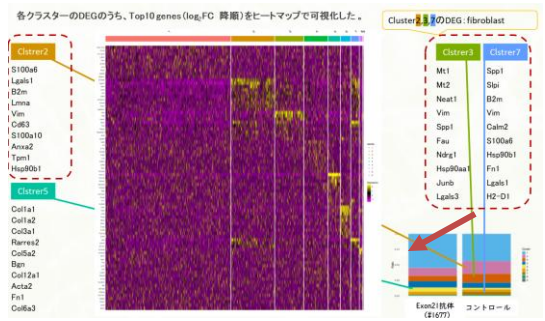


$CD44^{high}CD24^{low}$
= Cancer stem cell fractionation

Taniyama et al. Sci Rep. 2018

④ Inhibition of myCAF

Pathological periostin	・Activating myCAFs (structure) produces ECM such as collagen, promoting tumor stiffness and fibrosis (signal) activates CD44 and enhances TGF-b (space) forms a metastatic niche
Periostin antibody (PT0101)	- Strongly suppresses myCAF activity- Potential to reduce filling pressure in the tumor microenvironment, thereby directing anticancer drugs deeper

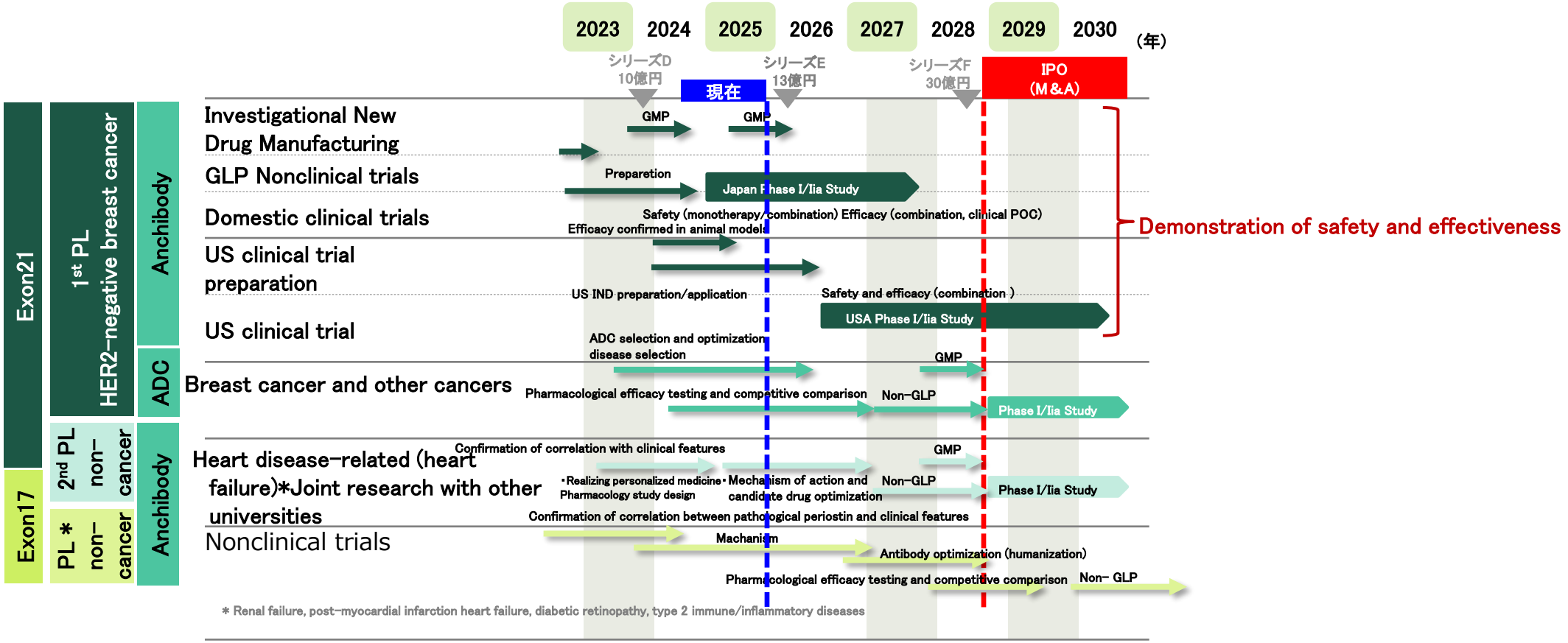


Unpublished data

Summary of this Drug Discovery Project and/or Biotechnology (4)

Overall development plan and clinical trial schedule

"① Human clinical research, ② Licensing, ③ Expansion of clinical research and development pipeline, ④ Continuous drug discovery and development through exit."



Summary of this Drug Discovery Project and/or Biotechnology (5)

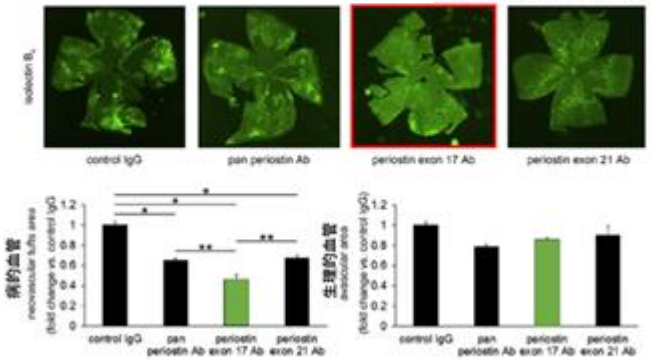
Therapeutic effects on non-cancer diseases: diabetic retinopathy, acute myocardial infarction, acute renal failure, inflammatory bowel disease, etc.

[Diabetic retinopathy (retinopathy of prematurity model)]

Exon17 Exon21

Pathological vascular depression

Exp Eye Res . 2016 Dec:153:133-140.



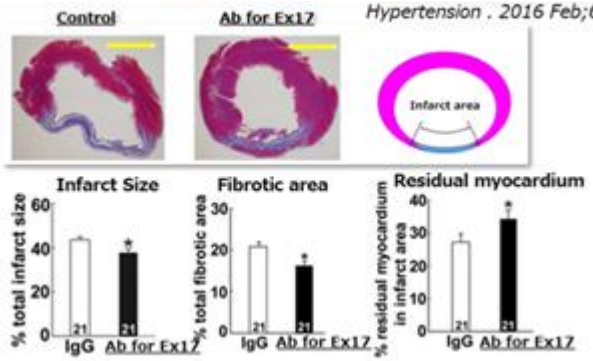
Among the current targets, VEGF is hardly secreted in the later stages of diabetic retinopathy, and analysis of numerous clinical samples has identified periostin as a target that is expressed in pathological retina but not in normal retina. Both the PN17 and PN21 antibodies inhibit pathological blood vessels, suggesting the possibility of novel therapeutic agents using bispecific antibodies.

[Acute myocardial infarction (rat myocardial infarction model)]

Exon17

Suppression of infarct size and increase of remaining myocardium

Hypertension . 2016 Feb;67(2):356-61.



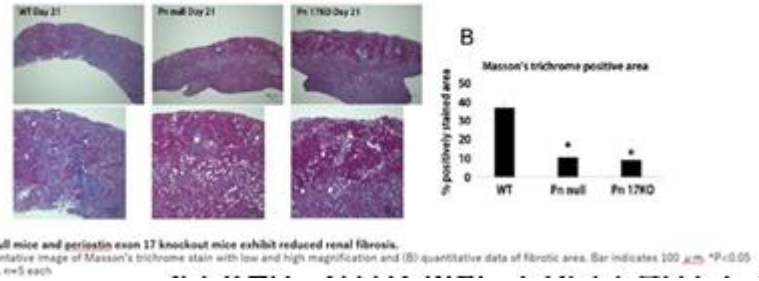
By administering the PN17 antibody the day after creating an acute myocardial infarction model in rats, analysis of the chronic phase confirmed a reduction in infarct size, improved cardiac function, and a significant increase in the remaining myocardium in the infarcted area. It is believed that simply administering two doses of the PN17 antibody in addition to existing treatments can suppress myocardial infarction and the onset of chronic heart failure.

[Acute myocardial infarction (rat myocardial infarction model)]

Exon17

Cells. 2022 Oct 27;11(21):3388.

A **Suppression of renal fibrosis**



Periostin null mice and periostin exon 17 knockout mice exhibit reduced renal fibrosis.

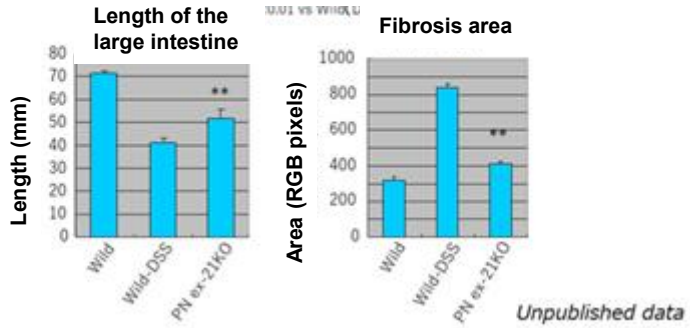
(A) Representative image of Masson's trichrome stain with low and high magnification and (B) quantitative data of fibrotic area. Bar indicates 100 μm. *P<0.05 vs WT mice, n=5 each

We have confirmed that administration of PN17 antibody to an acute renal failure model has an inhibitory effect on renal fibrosis.

[Inflammatory bowel disease (DDS colitis model)]

Exon21

Suppression of colon fibrosis



Unpublished data

It has been confirmed that administration of PN21 antibody to a DSS-induced inflammatory bowel disease model suppresses colon shortening and the area of fibrosis.

Advantage of this Project and/or Biotechnology (1)

Comparison with competing drugs

Our product is different in that we target pathological periostin, whereas other companies target both physiological and pathological periostin.

	Our antibody (PT0101/PT0201)	Pan-periostin antibody
Target	Pathological Periostin	All Periostin =Pathological & Physiological Periostin
Localization of Periostin	Lesion area (stroma)	Normal and Lesion area
Risk of safety*	Low	High
Efficacy	High	Low**

Physiological periostin is distributed throughout the body, so antibodies may be dispersed throughout the body. On the other hand, pathological periostin is secreted from tumors, so antibodies tend to accumulate locally.

Suppression of physiological periostin tends to increase cancer growth and may also induce side effects.On the other hand, suppression of pathological periostin shrinks cancer growth and may be more effective than suppressing both.

*Speculation from the phenotype of periostin knockout mice
**Prepartion of the similar antibody in-house based on the information in the patent

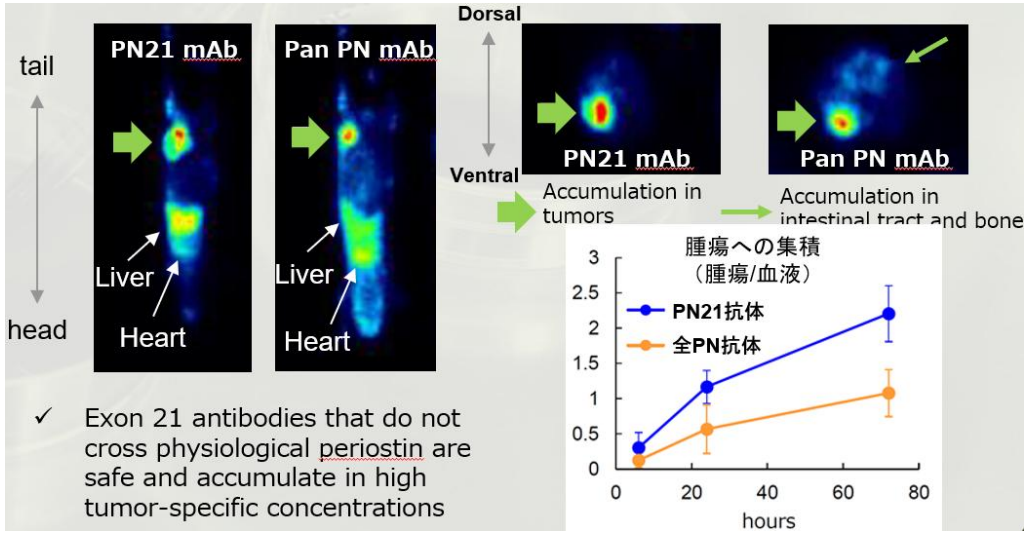
★Pan-periostin antibody uses the N-terminus of periostin as an antigen (recognizing the entire periostin). On the other hand, we use a different antibody that uses the C-terminus as an antigen (recognizing pathological periostin).

Advantage of this Project and/or Biotechnology (2)

Comparison of biodistribution and function between other companies' whole periostin antibodies and pathological periostin antibodies

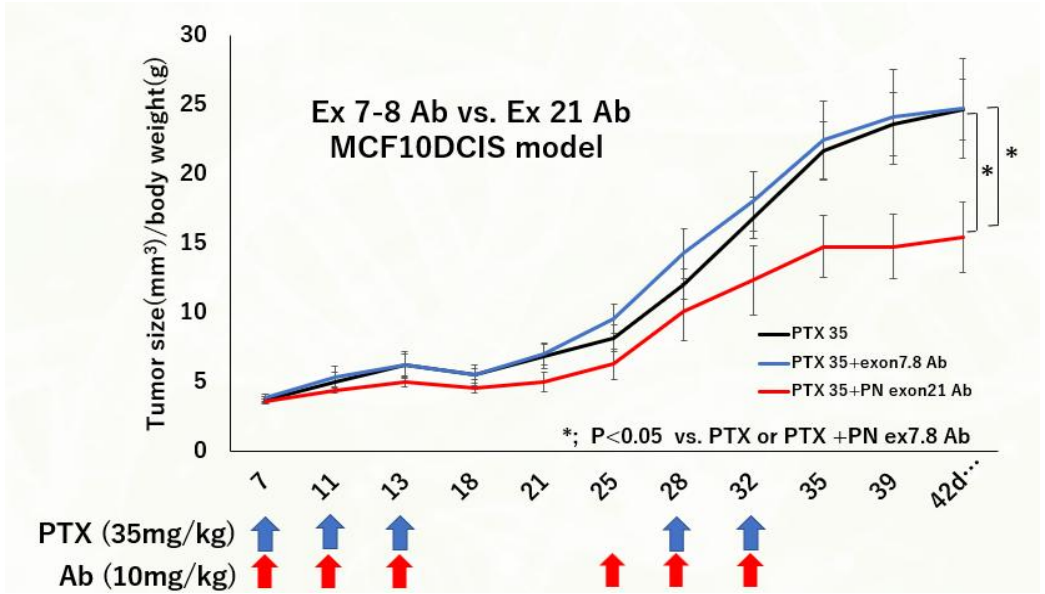
Biodistribution comparison with other companies' antibodies

The PN21 antibody binds only to pathological periostin present in the cancer microenvironment, whereas the whole-PN antibody also binds to physiological periostin, resulting in systemic distribution and tumor accumulation twice as high as the PN21 antibody.



Chemotherapy-resistant TNBC model

In a paclitaxel-based chemotherapy-resistant model, the PN21 antibody has a significant inhibitory effect, whereas the total PN antibody has a weak antitumor effect.

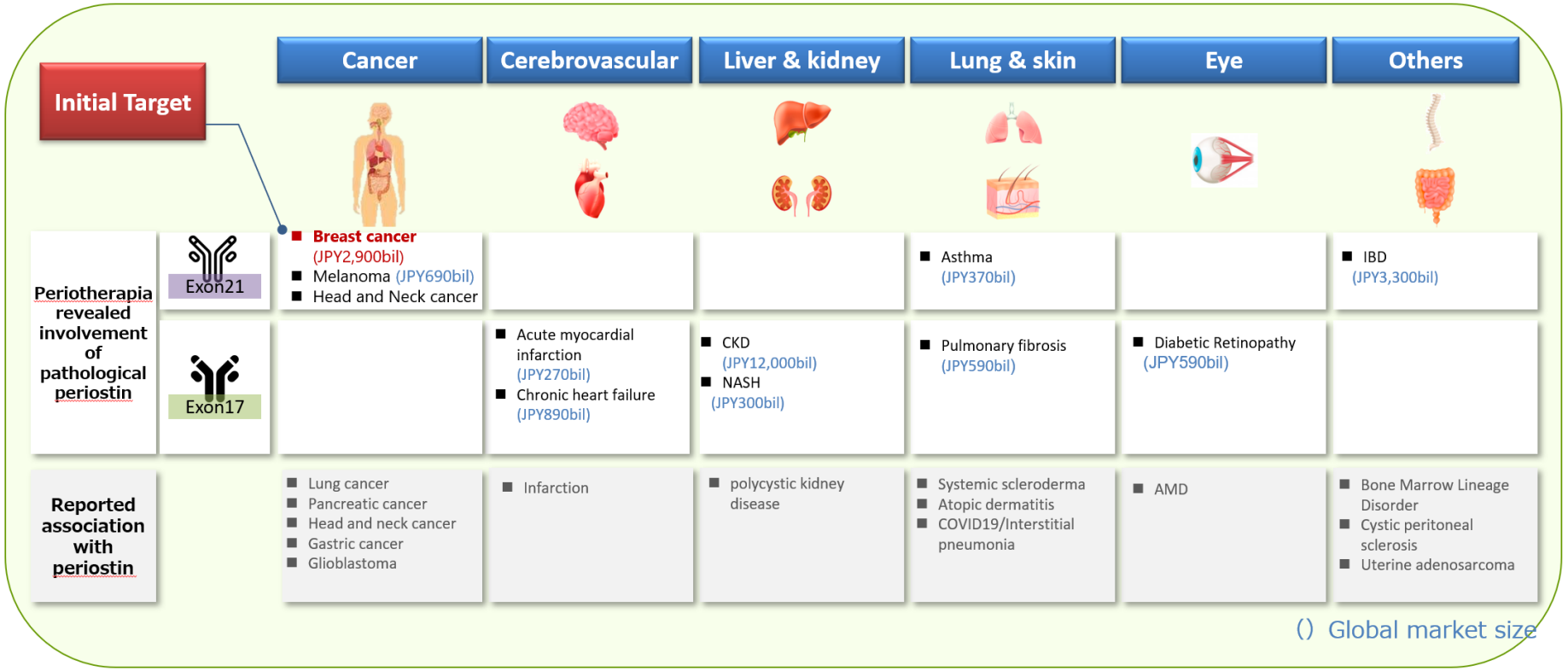


潜在的な対象疾患、治療領域 / 参考文献 / 特許等

I) Potential target diseases/therapeutic areas

Potential target disease and/or therapeutics area on this proposal

1st PL: (HER2-negative) breast cancer, malignant melanoma, head and neck cancer, and other malignant tumors.2nd PL: Suppression of heart failure after myocardial infarction, diabetic retinopathy, etc.



Potential target diseases, treatment areas / References / Patents, etc.

2) Key paper and/or

1. Osaka University Graduate School of Medicine News & Topics: Towards a breakthrough in cancer treatment! Clinical trials of a new antibody drug for metastatic and recurrent breast cancer - "PT0101" targets pathological periostin -https://www.med.osaka-u.ac.jp/archives/42863
2. Kanemoto Y et al. Expression of periostin alternative splicing variants in normal tissue and breast cancer. Biomolecules. 2024 Aug 31;14(9):1093. doi: 10.3390/biom14091093.
3. Fujikawa T et al. Periostin exon-21 antibody neutralization of triple-negative breast cancer cell-derived periostin regulates tumor-associated macrophage polarization and angiogenesis. Cancers (Basel) . 2021 Oct 11;13(20):5072. doi: 10.3390/cancers13205072.
4. Ikeda-Iwabu Y et al. Periostin short fragment including exon 17 via aberrant alternative splicing is required for breast cancer growth and metastasis. Cells 2021. Apr 14;10(4):892. doi: 10.3390/cells10040892
5. Nakazawa Y et al. Periostin blockade overcomes chemoresistance via restricting the expansion of mesenchymal tumor subpopulations in breast cancer. Sci Rep. 2018 Mar 5;8(1):4013. doi: 10.1038/s41598-018-22340-7.
6. Nakama T et al. Different roles played by Periostin splice variants in retinal neovascularization. Exp Eye Res. 2016 Dec;153:133-140
7. Taniyama Y et al. Selective blockade of periostin exon17 preservre cardiac performance in acute myocardial infarction. Hypertension, 2016 Feb;67(2):356-61.

3) Patent

International Publication Number: WO2007/077934Application Date: December 28, 2006Title of Invention: Anti-periostin Antibody and Prevention of Periostin-Related Diseases Containing the Antibody Applicant: Osaka University/Yoshiaki Taniyama

International Publication Number: WO2014/136910Filing Date: March 8, 2014Title of Invention: Antibody Encoded by Exon-21 Region of Periostin and Pharmaceutical Composition for the Prevention or Treatment of Inflammation-Related Diseases Comprising the Antibody Applicant: Osaka University/Yoshiaki Taniyama

International Publication Number: WO2023/106284
Application Date: December 6, 2022
Title of Invention: Antibody or Antigen-Binding Fragment
Applicant: Osaka University/Yoshiaki Taniyama

International Publication Number: 2025-005857 Application Date: January 16, 2025Title of Invention: Periostin Detection Method Applicant: Osaka University/
Yoshiaki Taniyama