FY2021 Japan Agency for Medical Research and Development
Project of Translational and Clinical Research Core Centers
**The Translational Research Program;
Strategic Promotion for Practical Application
of Innovative Medical Technology**

MAKE NEW STANDARDS.
東海国立大学機構

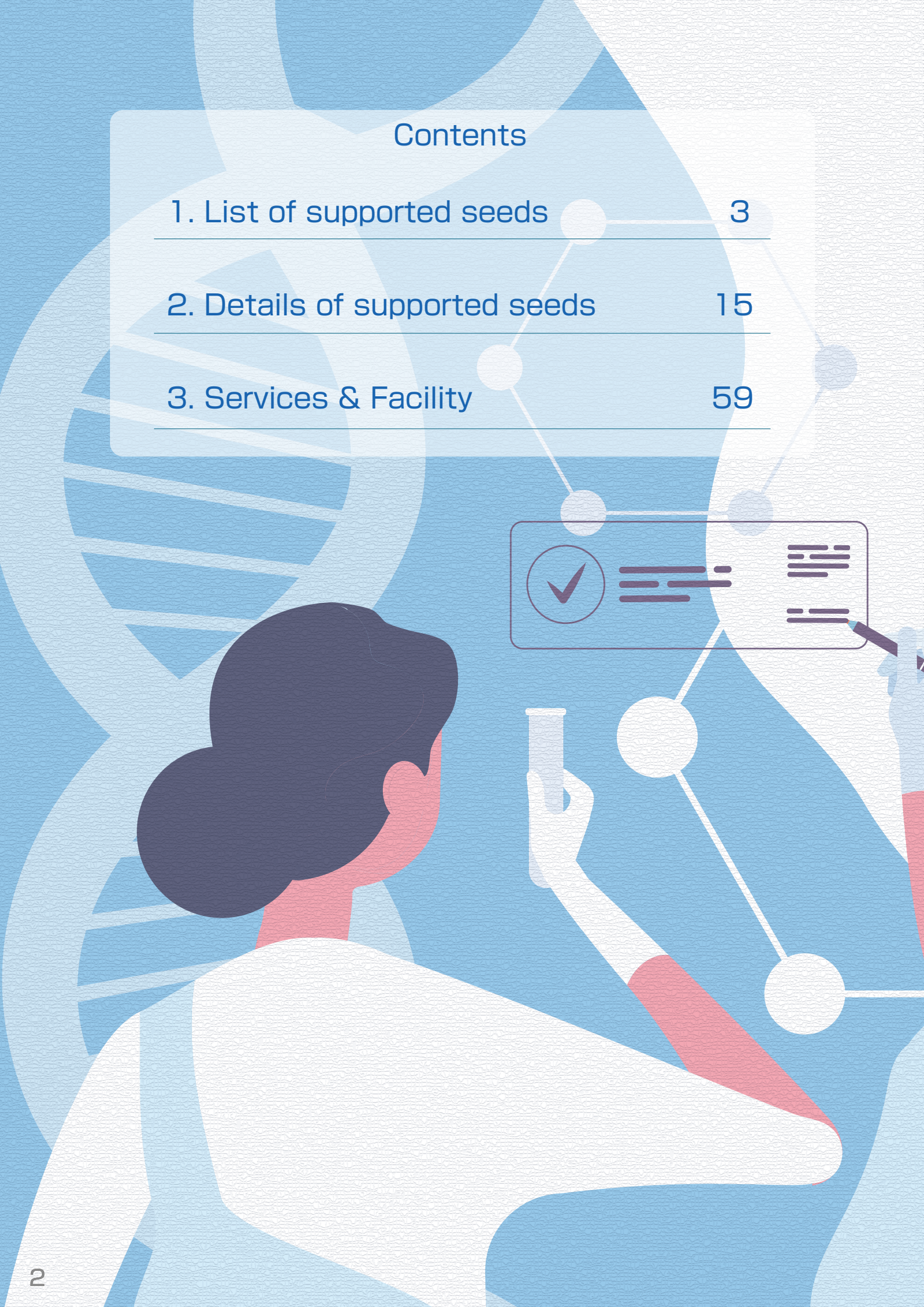
NAGOYA UNIVERSITY

Development of Advanced Medicine Portfolio 2022

Department of Advanced Medicine
Nagoya University Hospital

CAMCR & DCC

Contents



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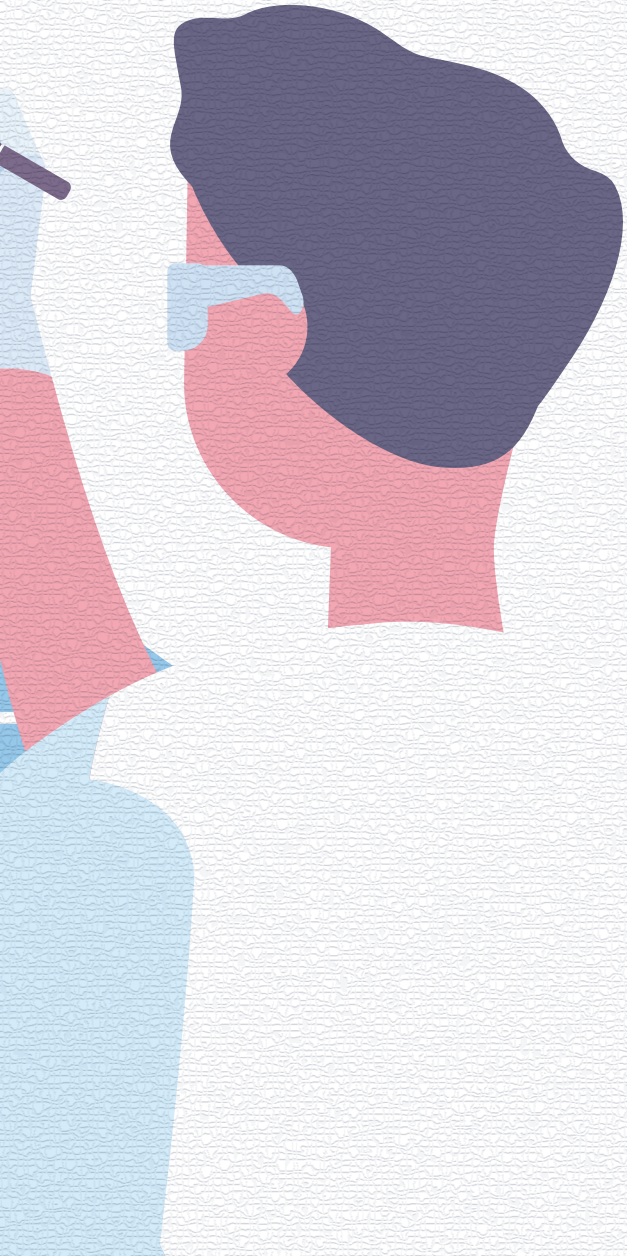

A 【Definition】 Patent application

Control Number	Project Title	Organization	Principal Investigator
A53	Development of new innovative targeted therapy by essential control of the HGF/MET axis in scirrhous gastric cancer	Kanazawa Medical University	Kazuo Yasumoto
A54	Development of novel antimicrobial coating for orthopaedic and dental implants with fluorine-added diamond-like carbon coating	Kanazawa Medical University	Masahito Kawaguchi
A56	Development of the novel anti-cancer drug targeting Pygo2	Gifu University	Kazuo Kuwata
A70	Development of ultra-precision synthesis of plasma-activated solution for peritoneal dissemination treatment	Nagoya University	Hiroaki Kajiyama
A73	Development of novel osteoanagenesis biodegradable hemostasis for bone marrow bleeding	Nagoya University	Yuji Narita
A74	New treatment for age-related diseases using LED devices with limited wavelengths	Nagoya University	Yoshihiro Nishida
A75	Development of therapeutic drug based on the molecular pathogenesis of Rett syndrome	Nagoya University	Norio Ozaki
A80	Development of a novel insulin sensitizer targeting adipose tissue macrophages	University of Toyama	Kazuyuki Tobe
A81	Development of novel anti-diabetic retinopathy drugs focusing on exacerbating molecular signaling cascades	University of Toyama	Seiji Yamamoto
A83	Development of function-enhanced T cells transfected with artificial T cell activation adapter molecule	Nagoya University	Hitoshi Kiyoi
A84	Novel drug screening system based on Reelin-dependent neuronal migration	Nagoya University	Norio Ozaki
A86	Development of novel culture system of MSC for renal disease	Nagoya University	Syouichi Maruyama
A87	Discovery of novel antigen of primary membranous nephropathy in Japanese patients	Nagoya University	Masashi Akiyama
A89	Development of kynurenine aminotransferase inhibitors as novel therapeutic agents for schizophrenia	Fujita Health University	Hidetsugu Fujigaki
A92	Development of treatments for refractory MEF2D acute lymphocytic leukemia targeting pre-B cell signals and transcriptional networks	Aichi Medical University	Shinobu Tsuzuki
A94	Development of new innovative targeted therapy by essential control of stromal HER1 and 4 in diffuse gastric cancer	Kanazawa Medical University	Kazuo Yasumoto
A95	Development of low molecular weight compounds against GVHD	Fujita Health University	Motoshi Suzuki
A96	Development of cell proliferation inhibitor targeting protease regulatory system downstream of receptor tyrosine kinase	Mie University	Masaki Inagaki
A97	Development of Anti-diabetic Drugs with Multifaceted Effects by Targeting Hepatokines	Kanazawa University	Kiyoaki Ishii

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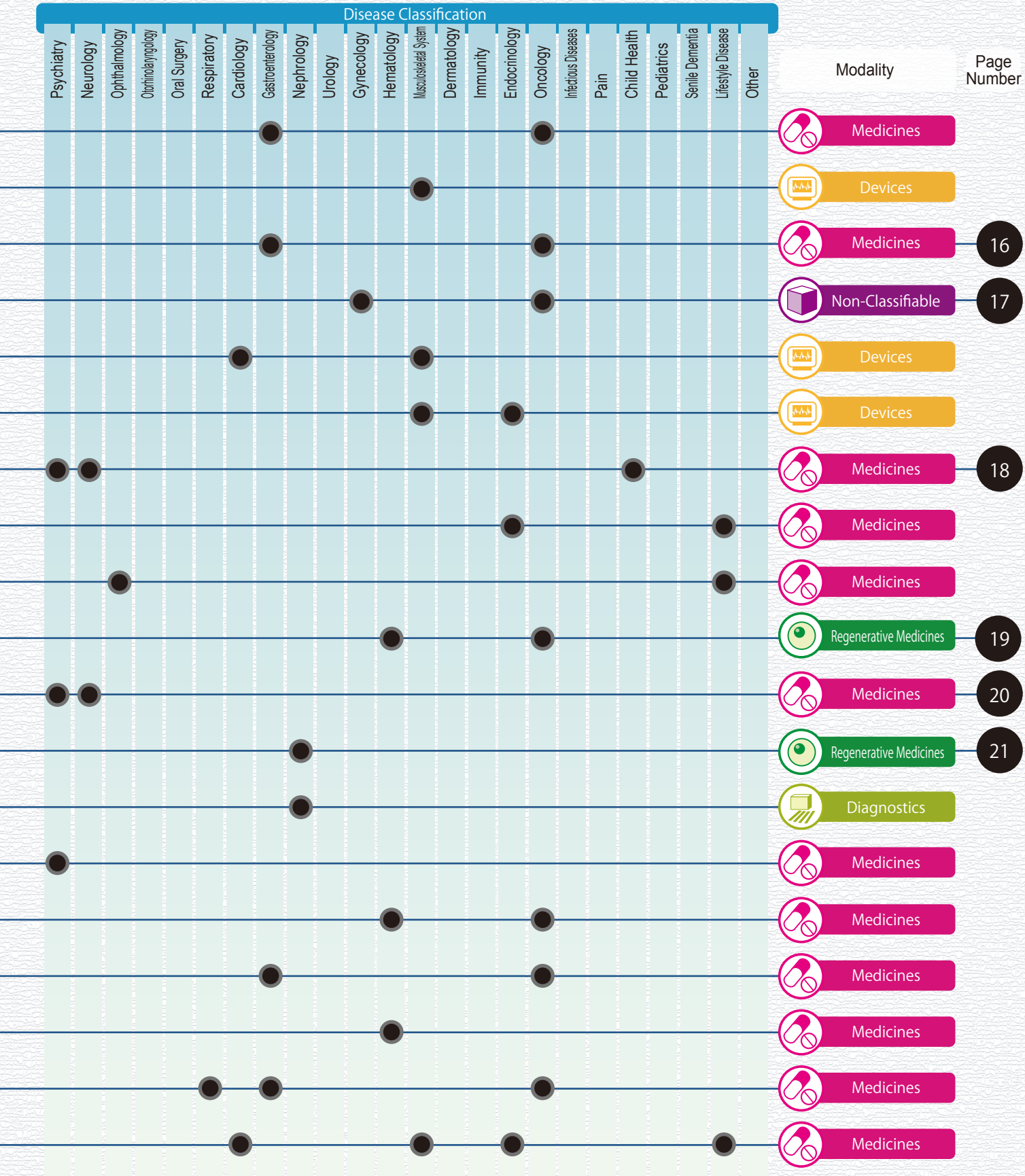

A 【Definition】 Patent application

Control Number	Project Title	Organization	Principal Investigator
A98	Discovery of urinary protein biomarkers for early detection of colorectal cancer	Nagoya City University	Takaya Shimura
A99	Cancer targeting phototherapy using antibody-drug conjugates	Nagoya University	Kazuhide Sato
A102	Development of novel drugs for KRAS-mutated cancer through inducing senescence	Nagoya University	Mitsuo Sato
A103	Development of human amnion derived mesenchymal stem cells for the treatment of refractory renal disease	Nagoya University	Syouichi Maruyama
A104	ELISA for measuring novel biomarker of SLE and lupus nephritis	Nagoya University	Syouichi Maruyama
A108	Development of small-diameter tissue engineered vascular grafts using synthetic elastin and their applications	Nagoya University	Ayae Sugawara-Narutaki
A109	Development of Antisense Oligonucleotides to Treat Gastrointestinal Malignancies	Nagoya University	Mitsuro Kanda
A111	Development of therapy for polyglutamine diseases using lipid nanoparticle-delivered siRNA duplexes targeting CAG expansions	Nagoya University	Masahisa Katsuno
A113	Development of a novel treatment with plasma-activated solution for intractable skin ulcer	Nagoya University	Hiroaki Kajiyama
A114	Development of wirelessly powered multi-channel neurostimulator for connecting peripheral nerve with machine	Nagoya University	Katsuhiro Tokutake
A115	The development of a real-time monitor for laser thrombolytic therapy	Hamamatsu University School of Medical	Kazuo Umemura
A116	Development of T cell receptor gene-modified T cells for liver cancer immunotherapy	Kanazawa University	Eishiro Mizukoshi
A117	Development of NanoSuit immunochromatography kit to identify several pathogens with high sensitivity	Hamamatsu University School of Medical	Takahiko Hariyama
A118	Automated Zebrafish-Based Drug Discovery System for Cancer Precision Medicine	Mie University	Toshio Tanaka
A119	Research and development on a therapeutic agent for cystic lymphangioma	University of Toyama	Seiji Yamamoto
A120	Identification of a novel therapeutic target for prostate cancer	Aichi Medical University	Motohiko Sato
A121	Development of peptide targeting FGFR2 amplified gastric cancer	Aichi Cancer Center Research Institute	Hiromichi Ebi
A122	Screening and validation of drugs for converting pattern-recognition receptor RAGE to a soluble decoy form	Kanazawa University	Yasuhiko Yamamoto
A123	Development of cell-permeable proteins targeting oncogenic RAS	Gifu University	Ryo Honda

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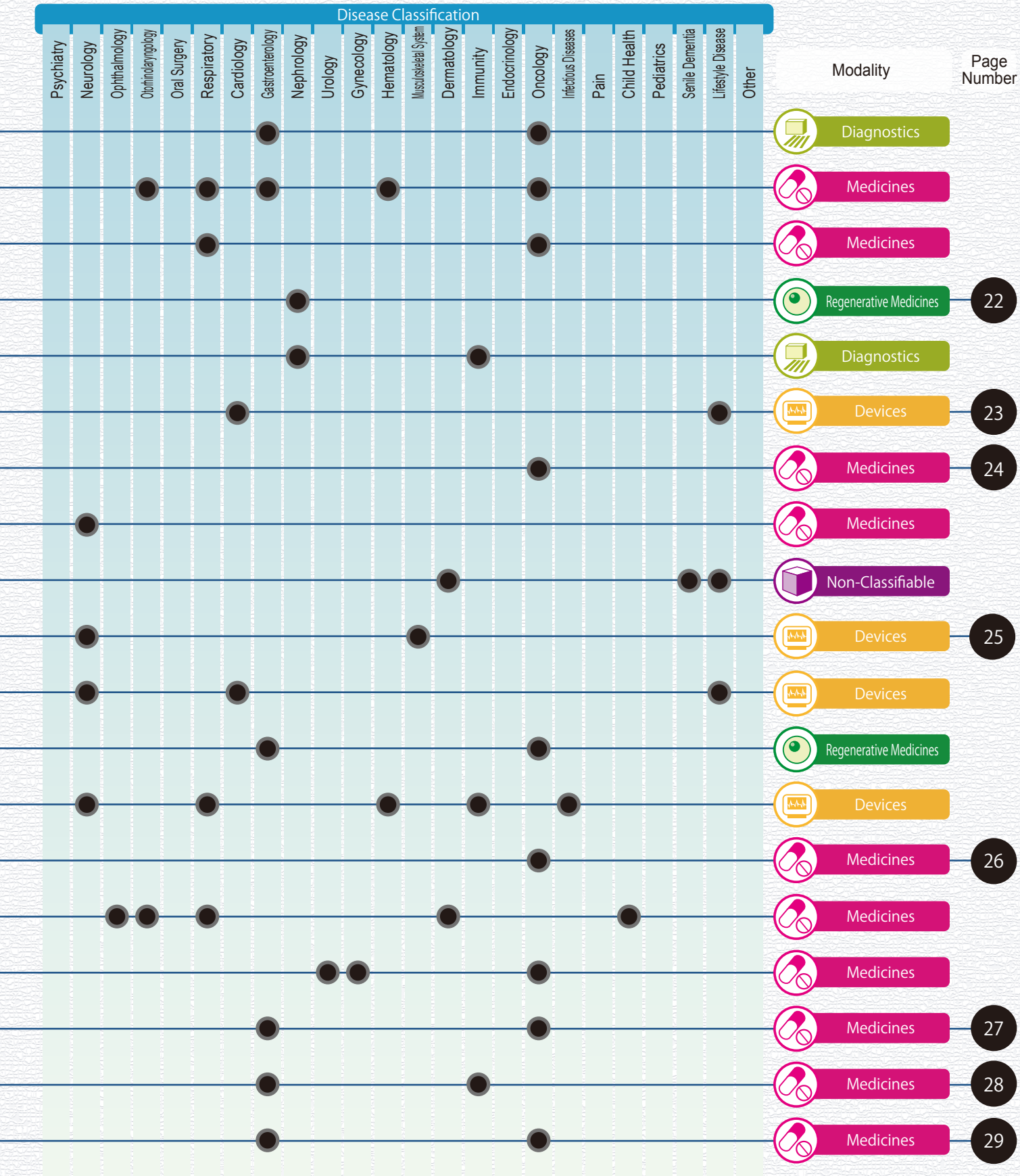

A 【Definition】 Patent application

Control Number	Project Title	Organization	Principal Investigator
A124	6-formylindolo[3.2-b]carbazole for highly selective photodynamic therapy against basal cell carcinoma	Nagoya City University	Motoki Nakamura
A125	Development of a rapid and easy identification system for neoantigen-specific TCR	University of Toyama	Hiroshi Hamana
A126	Cancer drugs that inhibit adipocyte-derived secreted factors	Fujita Health University	Yohei Shimono
A129	A novel therapeutic device using deep UV for endoscopic and laparoscopic surgery	Nagoya University	Toshio Kokuryo
A130	Development of therapeutic agents for osteoclast proliferative diseases	Nagoya University	Yoshihiro Nishida
A132	Development of novel serum tumor markers for various types of solid cancers	Nagoya University	Mitsuro Kanda
A134	Development of a drug that increases the efficacy of immune checkpoint inhibitors	Nagoya University	Atsushi Enomoto
A136	The challenge of developing a overwhelmingly minimally invasive treatment method for patients with pneumothorax	Nagoya University	Shota Nakamura
A137	Development of a metabolomics-based panel test that can discriminate individual differences in childhood cancer (neuroblastoma)	Nagoya University	Akinari Hinoki
A138	Development of inflammasome-targeted therapies for inflammatory bowel disease	Nagoya University	Keiko Maeda
A140	Detection of occult-bacterial translocation by bacterium-specific ribosomal RNA-targeted RT-	Nagoya University	Yukihiro Yokoyama
A142	Development of new lead proteins for pro-angiogenic therapy	Fujita Health University	Kentaro Tsukamoto
A143	Development of diagnostic imaging equipment using microwave imaging for breast cancer detection	Aichi Medical University	Kimihito Fujii
A145	Drug discovery of novel DPP8 inhibitor as an anti-hematological malignancy agent	University of Toyama	Tsutomu Sato
A148	Development of next-generation near-infrared photoimmunotherapy	Nagoya University	Kazuhide Sato
A149	Metabolite analysis of biliary atresia to elucidate the etiology and search for disease markers	Nagoya University	Hiroo Uchida

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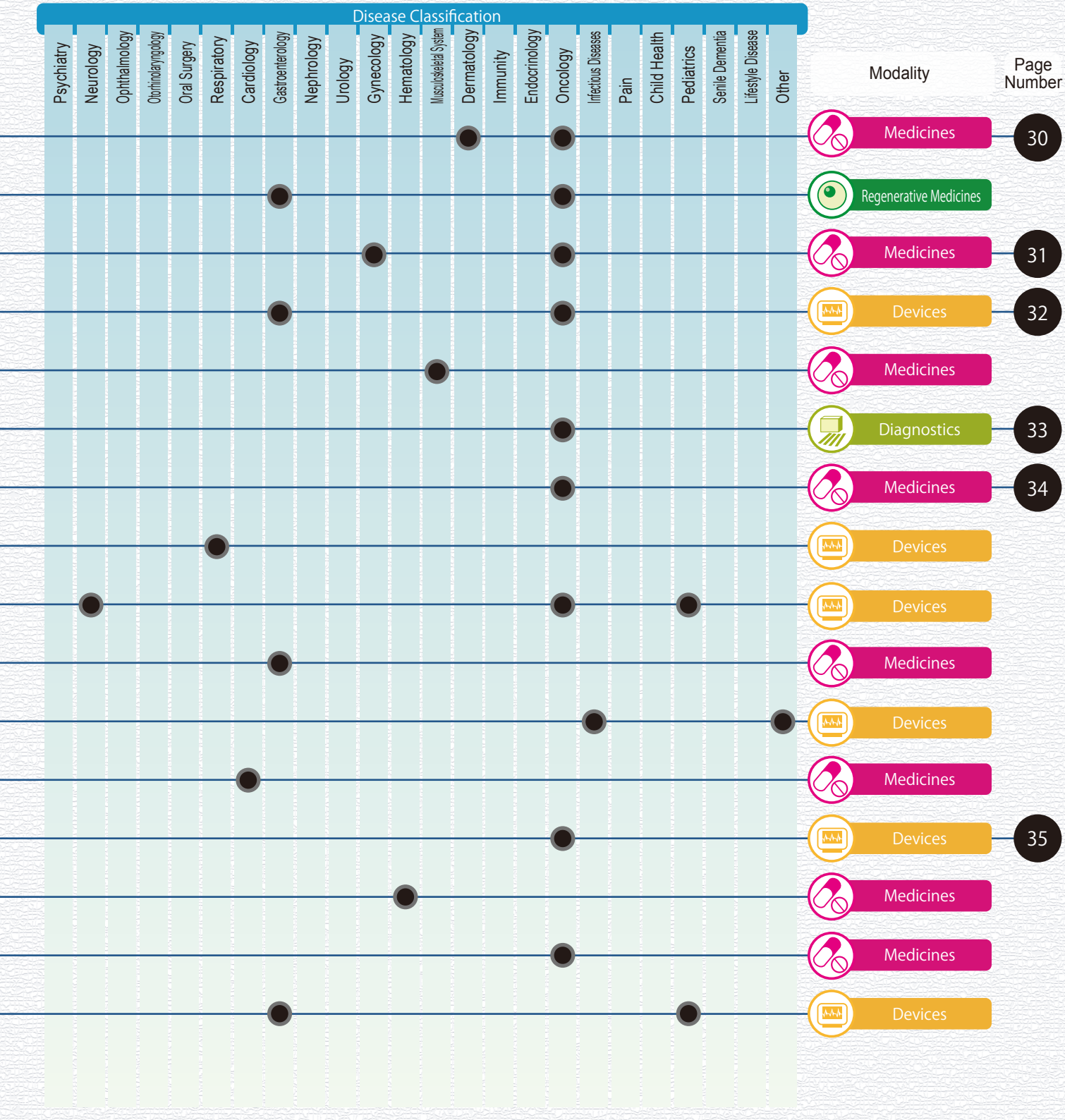

B 【Definition】Non-clinical POC

Control Number	Project Title	Organization	Principal Investigator
B25	Research and Development of Scleroderma Treatment with UV-A1 Light Using High Power UV-LED	Nagoya City University	Akimichi Morita
B36	Patient-Derived Xengraft Zebrafish Model(PDXZ) for Companion Diagnostics and Drug Discovery	Mie University	Toshio Tanaka
B51	Development of a monoclonal antibody to treat gastric cancer	Nagoya University	Mitsuro Kanda
B52	The development of novel therapies using Muse cells for neurodevelopmental disorders in infants with fetal growth restriction	Nagoya University	Masahiro Hayakawa
B53	Development of a novel real-time artificial intelligence evaluation system for voice disorders	Nagoya City University	Tetsuji Sanuki
B55	Development of novel custom made implants for reconstruction after bone tumor resection	University of Toyama	Taketoshi Yasuda
B56	Development of regenerative therapy using pluripotent stem cells (Muse cells) to repair lung injury in neonates	Nagoya University	Yoshiaki Sato
B61	Non-clinical trial of a long-acting oxytocin analogue for the treatment of autism spectrum disorders	Kanazawa University	Shigeru Yokoyama
B63	Clinical practical application study of intestinal bacterial protease measurement kit aiming at identification of high-risk group of liver carcinogenesis	Kanazawa University	Eishiro Mizukoshi
B64	Development of antisense nucleotides specialized for treatment of peritoneal metastasis of gastric cancer	Nagoya University	Mitsuro Kanda
B66	Development of artificial articular cartilage and intervertebral disc	Mie University	Koji Akeda
B68	Study of discovery of drugs reducing endoplasmic reticulum stress of familial neurohypophysial diabetes insipidus	Nagoya University	Hiroshi Arima
B69	Development of a PANORAMIC VISION SYSTEM to visualize the whole chest cavity	Nagoya University	Shota Nakamura
B71	Disease modifying therapy by antisense modulation of tau isoforms	Nagoya University	Shinsuke Ishigaki
B73	A new intra-ocular sustained release system for bioactive proteins	Nagoya City University	Tsutomu Yasukawa
B74	Urinary miRNA biomarker for early detection of gastrointestinal cancer	Nagoya City University	Takaya Shimura
B76	Development of T-cell exosome drugs for inhibiting tumor progression	Mie University	Naohiro Seo

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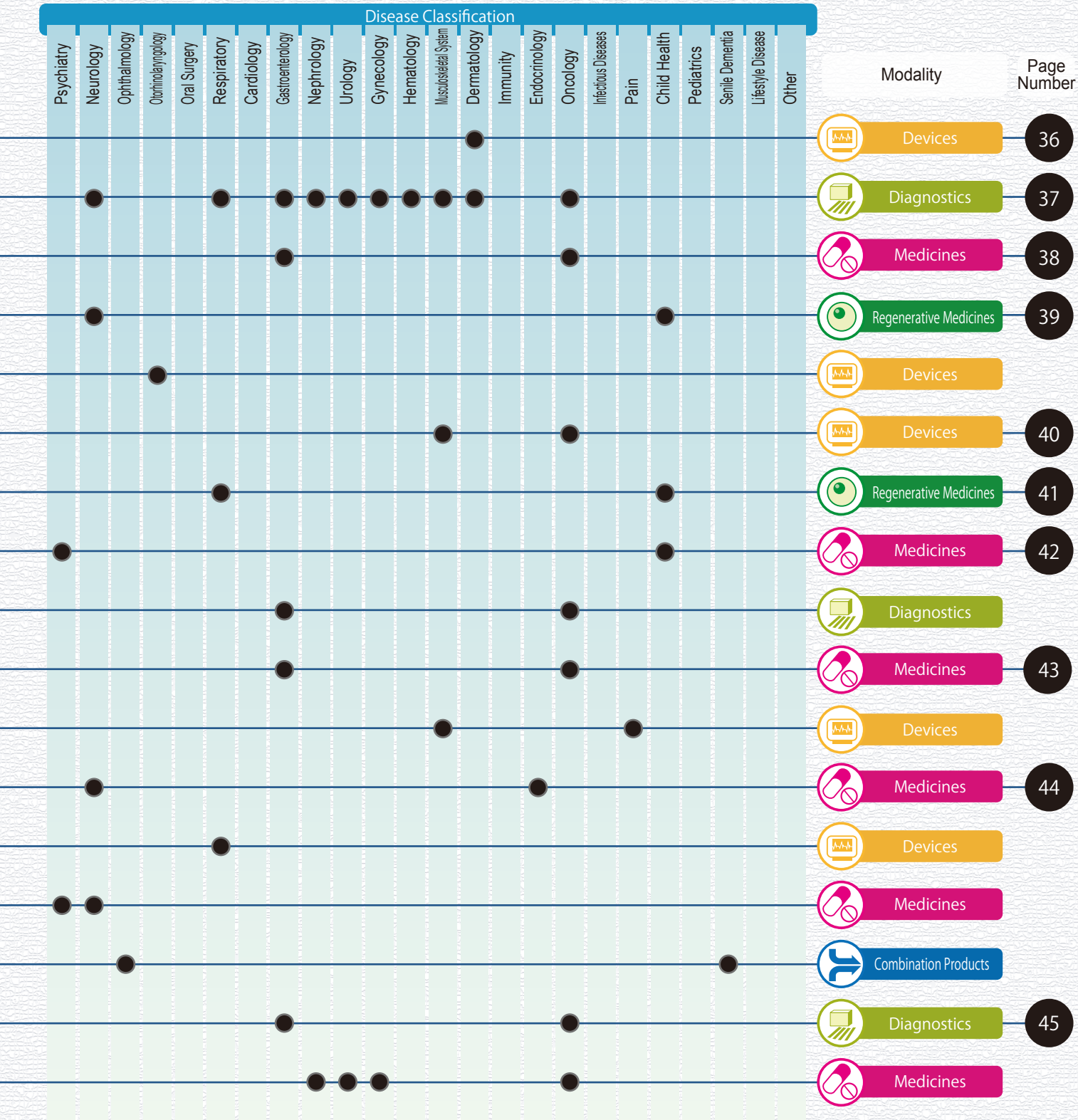

C 【Definition】 Clinical POC

Control Number	Project Title	Organization	Principal Investigator
C02	Development of Virus Specific Cytotoxic T cells Therapy for Refractory Viral Infection after Allogeneic Hematopoietic Stem Cell Transplantation	Nagoya University	Yoshiyuki Takahashi
C14	Multicenter clinical trial of the Patient-Specific Cardiac Support Device (CSD) with less constraint on Right Ventricle (RV) for Dilated Cardiomyopathy	Nagoya University	Toshiaki Akita
C16	Alternative treatment of combined physical therapy for postoperative lymphedema	Nagoya University	Hitoshi Hirata・Katsuyuki Iwatsuki
C22	Research and development for the medical treatment of achondroplasia by attenuating FGFR3 signaling	Nagoya University	Masaki Matsushita
C25	Multicenter Clinical Trial of Hyper Dry Human amnion membrane (HD amnion) as Medical Device for Therapeutic Use	University of Toyama	Toshiko Yoshida
C26	Research aimed at creating the development of devices for hyperthermia therapy for superficial lesions	Nagoya University	Nobuhisa Yoshikawa
C27	Phase I study of piggyBac transposon mediated chimeric antigen receptor gene modified T cells for CD19 positive acute lymphoblastic leukemia	Nagoya University	Yoshiyuki Takahashi
C29	Clinical study to evaluate the safety of co-injection of adipose-derived MSC and cord blood hematopoietic stem cells into the bone marrow cavity	Aichi Medical University	Takayuki Nakayama
C30	A multi-center, single-arm clinical study of the efficacy and safety of rituximab in CIDP patients with IgG4 autoantibodies	Nagoya University	Masahiro Iijima
C31	Development a novel regenerative treatment for perinatal brain injury with Muse cells - Exploratory investigator-initiated clinical trial -	Nagoya University	Yoshiaki Sato
C33	Development of allogeneic adipose derived stem cells therapy for the treatment of IgA nephropathy	Nagoya University	Syouichi Maruyama
C34	Physician-initiated clinical trial on the efficacy and safety of auranofin for aggressive fibromatosis	Nagoya University	Yoshihiro Nishida
C37	Open-label phase I/II investigator-initiated clinical trial based on a drug repositioning approach that reprograms the stroma of pancreatic cancer	University of Tokyo	Mitsuhiro Fujishiro
C39	Multicenter clinical trial of the Patient-Specific Cardiac Support Device (CSD) with less constraint on RV for Dilated Cardiomyopathy	Nagoya University	Toshiaki Akita
C40	Protocol preparation of investigator-initiated clinical trial to assess efficacy and safety of mexiletine hydrochloride for the patients with spinal and bulbar muscular atrophy	Nagoya University	Shinichiro Yamada
C41	Preparation of an Investigator-Initiated Clinical Trial Protocol for Idiopathic Membranous Nephropathy with Nephrotic Syndrome Using Rituximab	Nagoya University	Akihito Tanaka
C42	Development of novel therapies targeting pulmonary microthrombosis of coronavirus disease 2019	Nagoya University	Yukari Goto
C43	Basket study of afatinib maleate (BIBW2992) in patients with solid tumors harboring NRG1 fusion for evaluating efficacy and safety	Nagoya University	Masahiro Morise
C44	A placebo-controlled, double-blind crossover study investigating the ameliorative effect of shakuyakukanzoto on paclitaxel (Tri-weekly)-induced muscle pain and arthralgia	University of Toyama	Akitoshi Nakashima

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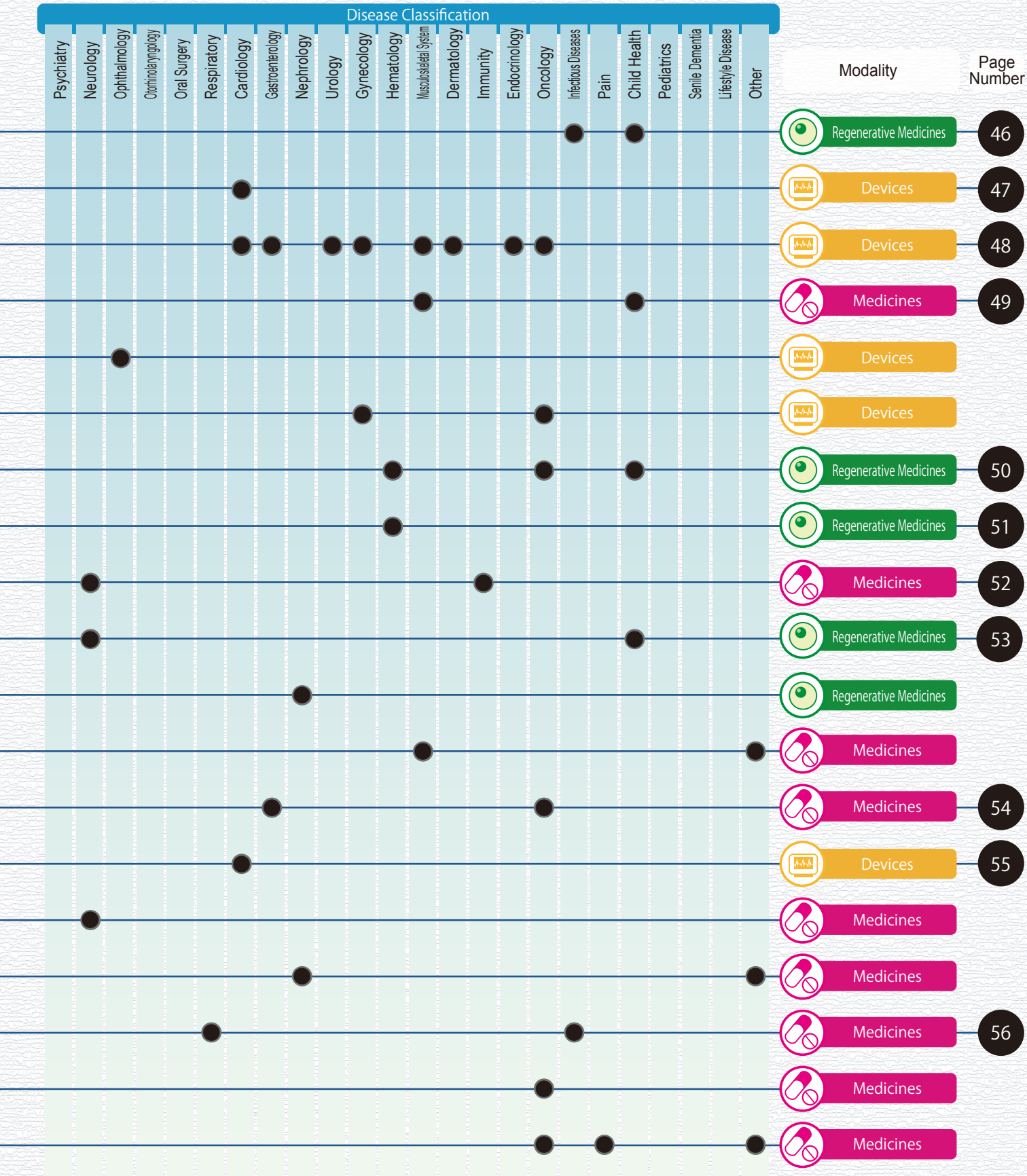

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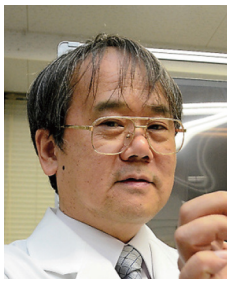


Project Title

Development of the novel anti-cancer drug targeting Pygo2

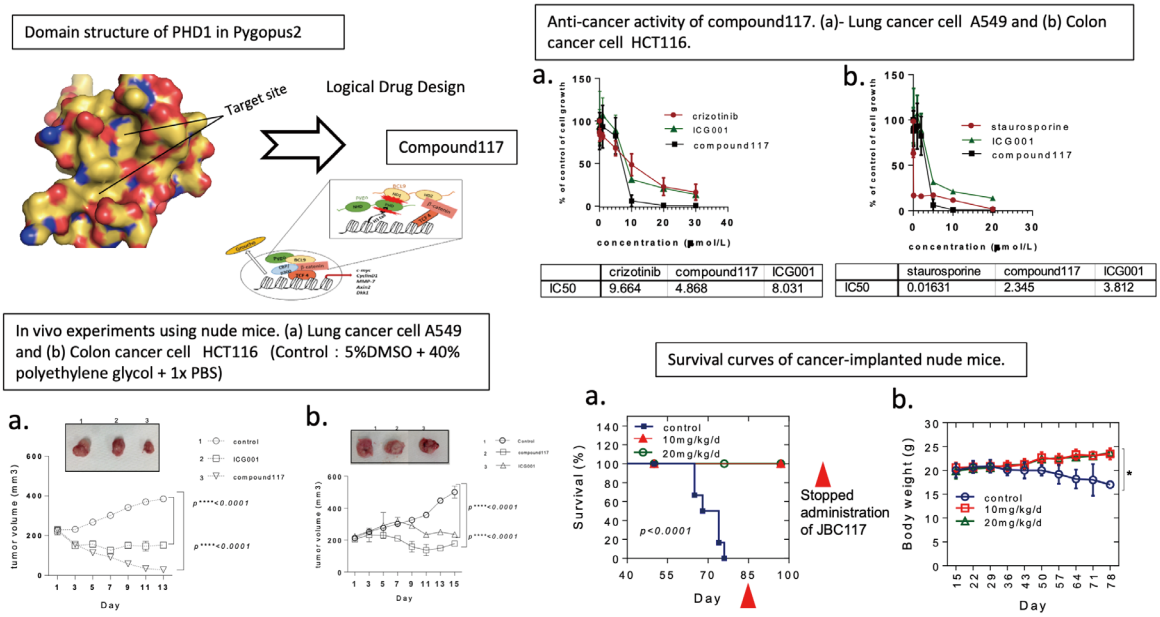
Organization

Gifu University

Principal Investigator

Kazuo Kuwata

Novel anti-cancer drug targeting Pygopus2



IC50	crizotinib	compound117	ICG001
	9.664	4.868	8.031

IC50	staurosporine	compound117	ICG001
	0.01631	2.345	3.812

Target Disease (Applications)	Lung Cancer
Abstract	Pygopus2 (Pygo2) is a component of the Wnt signaling pathway, which is required for β-catenin mediated transcription. Here, we found JBC117 interacts with D339, A348, R356, V376 and A378 in PHD in Pygo 2 corresponding to the binding sites with H3K4me and/or HD1, and has strong anti-cancer effects. For colon (HCT116) and lung (A549) cancer cell lines, IC50 values were 2.6 ± 0.16 and 3.3 ± 0.14 μM, respectively, while 33.80 ± 0.15 μM for the normal human fibroblast cells. JBC117 potently antagonized the cellular effects of β-catenin-dependent activity and also inhibited the migration and invasion of cancer cells. In vivo studies showed that the survival time of mice was significantly prolonged by the subcutaneous injection of JBC117 (10 mg/kg/day). In conclusion, this compound that was optimized from the lead structure of JBC117 is a novel anti-cancer compound targeting the PHD finger of Pygo2 and has a therapeutic effect against colon and lung cancer.
Advantages	Unprecedented and unparalleled anti-cancer activity against lung cancer.
Patent Information	Japanese patent no. 2016-020586
Market Overview	No. of patients: ~100,000
Stage of Development	Synthetic Expansion

Project Title

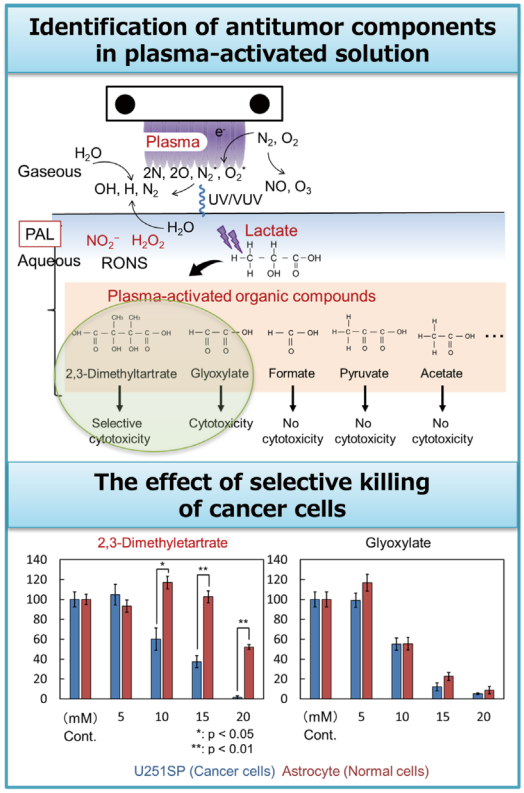
Development of ultra-precision synthesis of plasma-activated solution for peritoneal dissemination treatment

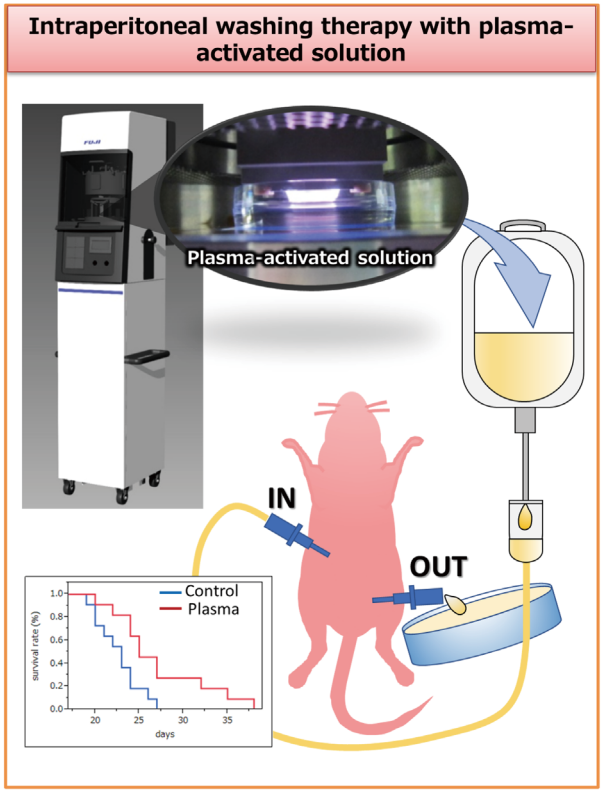
Organization

Nagoya University

Principal Investigator

Hiroaki Kajiyama





Target Disease (Applications)	Peritoneal dissemination of cancers, e.g. ovarian cancer
Abstract	At Nagoya University, we have been promoting research towards the creation of plasma medical science and its clinical application. We found that a culture solution irradiated with an ultra-high density plasma (what we call plasma-activated medium, PAM) exhibited antitumor effects. We further developed plasma-activated Ringer's lactate solution (PAL). We identified an antitumor factor in PAL, which is plasma-activated sodium lactate, and long-term stability of PAL.
Advantages	Plasma-activated solutions exhibit antitumor potential. It is effective for the treatment of microdissemination.
Patent Information	PCT / JP2015 / 006419 and 6 other related patent applications were filed. Regarding the basic patent, Japanese Patent No. 6099277 and 6381111 were reached.
Market Overview	Peritoneal dissemination such as ovarian cancer, gastric cancer, pancreatic cancer, mesothelioma, etc. is the subject, and there is currently a demand for new treatments because there is no effective treatment.
Stage of Development	PAL prepared using a plasma-activated solution preparation apparatus developed as medical equipment by Fuji Corp. was intraperitoneally administered to the mouse model of ovarian cancer, and we found that this significantly extended the overall survival rate and might be effective to improve clinical outcomes of early-stage ovarian cancer without severe adverse effects. We have demonstrated the required specification of the PAL for cancer treatment and its effective protocol of clinical applications.

Project Title

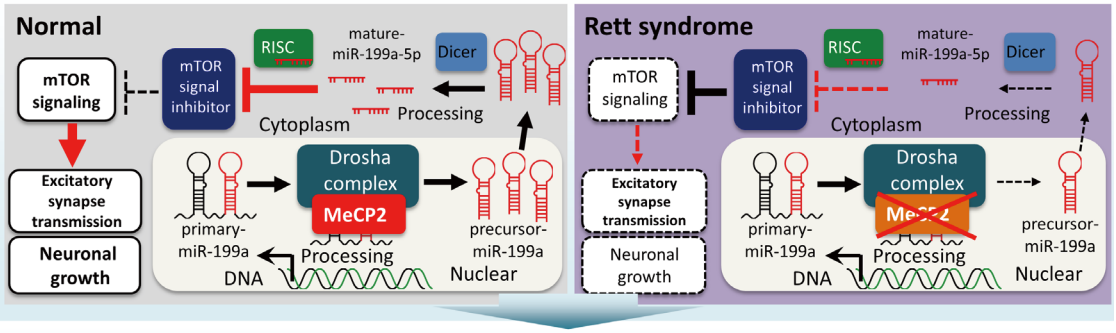
Development of therapeutic drug based on the molecular pathogenesis of Rett syndrome

Organization
Nagoya University

Principal Investigator
Norio Ozaki

Development of therapeutic drug based on the molecular pathogenesis of the Rett syndrome

Identification of the signaling pathway that is important for the pathophysiology
Tsujimura K. et al. *Cell Rep.* (2015)



The exploration of therapeutics drug based on the molecular mechanism
Screening system using patients derived iPSCs, *in vitro* screening system

Drug evaluation *in vivo* using Rett syndrome model mice

Drug evaluation using other disease model cells, tissues, mice

Development of therapeutic drug for broad developmental disorders and epilepsy

Target Disease (Applications)	Autism spectrum disorders including Rett syndrome, Epilepsy
Abstract	Purpose of this project is development of therapeutic drug against the broad mental disorders and elucidation of common molecular mechanisms of Rett syndrome and other developmental diseases based on the molecular mechanism of Rett syndrome.
Advantages	Molecular mechanisms of Rett syndrome has not been elucidated. For this reason, effective drugs have not been developed so far. Since this project performs development of therapeutic drugs based on the molecular mechanism, which are elucidated recently, of Rett syndrome, development of effective drugs are anticipated.
Patent Information	Patent application 2019-46718 (March 14th, 2019) Detection method of microRNA processing activity and its application
Market Overview	Autism spectrum disorders including Rett syndrome (1 million in Japan), epilepsy (1 million in Japan) Applicable to a wide range of neurodevelopmental disorders, and is highly marketable
Stage of Development	Stage of construction of screening systems Complete the construction of the evaluation system and carry out compound screening. It is necessary to expand the model system (cells, mice).

Project Title

Development of function-enhanced T cells transfected with artificial T cell activation adapter molecule

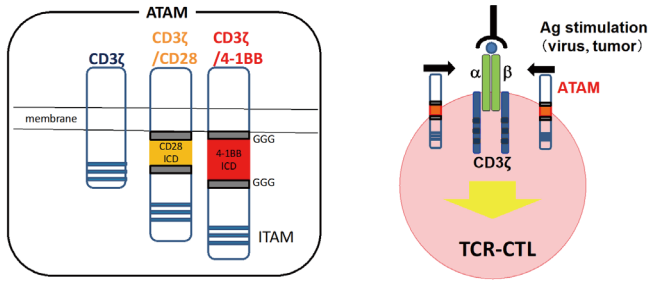
Organization

Nagoya University

Principal Investigator

Hitoshi Kiyoi

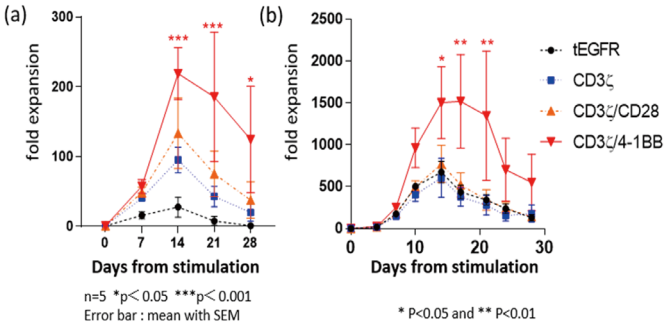
・Generation of artificial T cell activating molecule : ATAM



Structure of artificial T cell activating molecule (ATAM) and proposed functional mechanism

① Upon TCR stimulation
② gene-transduced ATAM assembles with TCR and forms a complex
③ transmit enhanced intracellular signals through CD28 or 4-1BB intracellular domain (ICD)

TCR-CTL transduced with ATAM which consists of basic component from CD3ζ
→ATAM assembles with TCR complex upon Ag stimulation
→No need for TCR affinity modification, which may lead unwanted CTL functional alteration



(a) Proliferation of CMV specific T cells
Upon Ag stimulation, ATAM with 4-1BB ICD showed better proliferation than that with CD28 ICD
(b) Proliferation of NY-ESO-1 TCR-T transduced with ATAMs
After transduction of NY-ESO-1 and ATAM simultaneously, CTLs were stimulated with Ag. ATAMs with 4-1BB ICD showed better expansion again

Target Disease (Applications)	Malignant tumor with tumor-specific antigen, such as NY-ESO-1 or WT-1 Pancreas cancer, acute myeloid leukemia, or myelodysplastic Syndrome
Abstract	TCR-T therapy using T cells transfected with a T cell receptor gene that recognizes cancer-specific antigens is being applied clinically, however, it only gives T lymphocytes cancer antigen specificity. Currently the activation signal necessary for overcoming the tumor microenvironment and immune tolerance is not sufficiently developed. We showed that the simultaneous adapter molecule transduction for the signal enhancement increases the proliferation and antitumor effect after antigen specific stimulation. (Miyao K et al. Cancer Immunology Research 2018)
Advantages	We can increase the intracellular signals after antigen recognition, which leads better T cell proliferation without TCR modification. There is no useful competitive technology that can enhance the signal after antigen recognition in TCR-T.
Patent Information	PCT/JP2017/022414
Market Overview	Pancreatic cancer is an intractable disease: approx 30,000 people die annually. There are similar numbers of patients in acute myelogenous leukemia and myelodysplastic syndrome.
Stage of Development	Preclinical stage We carried out experiments to confirm the enhancement of antitumor effect in vivo. We want to get a development partner and proceed to practical application.

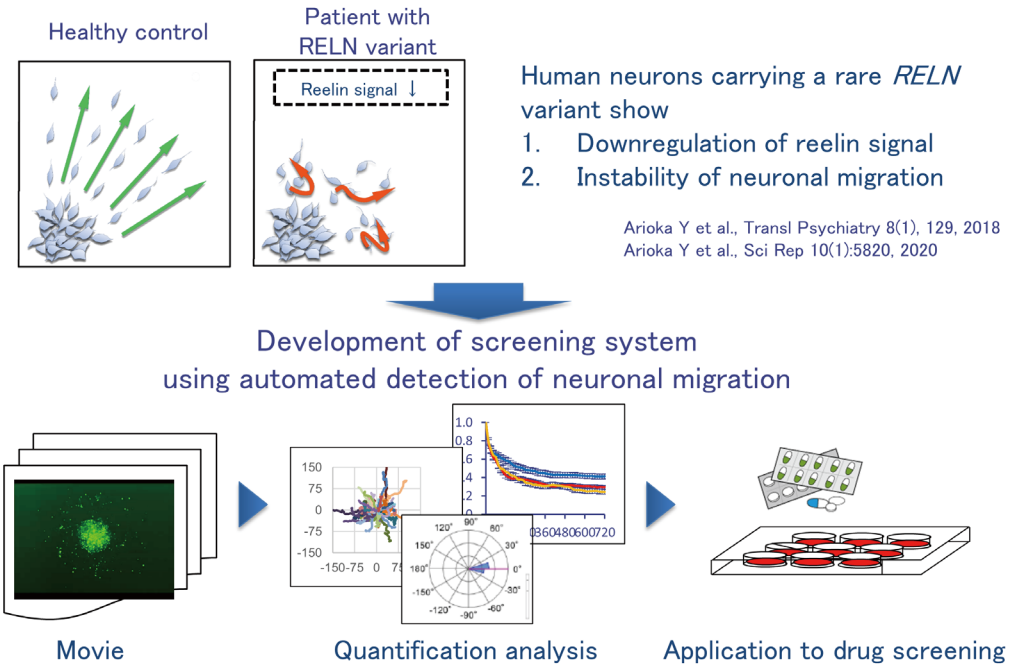
Project Title

Novel drug screening system based on Reelin-dependent neuronal migration

Organization
Nagoya University

Principal Investigator
Norio Ozaki

Novel Drug Screening System Based on Reelin-dependent Neuronal Migration



Target Disease (Applications)	Mental disorders (e.g. schizophrenia, autism spectrum disorders)
Abstract	Reelin is a huge secreted protein that is extensively involved in brain function from the developmental stage (e.g. neuronal migration) to the adult stage (e.g. synaptic plasticity). Therefore, we focus on reelin as a drug discovery target for mental disorders. The purpose of this study is establishment of a novel drug screening system that targets reelin-dependent pathology, using patient-derived neurons.
Advantages	Many pharmacy companies are engaged in drug discovery using iPS derived from patient with mental disorders, but it has not yet come true in mental disorders. An evaluation system that can capture the dynamic alterations in patient-derived neurons is essential. Our system solves this issue.
Patent Information	Patent application 2017-82600 (April 19th, 2017), PCT/JP2018/15304(2018/4/11): METHOD FOR PRODUCING DOPAMINERGIC NEURONS Patent application 2018-35758 (February 28th, 2018), PCT/JP2018/047146(2018/12/21): DRUG EVALUATION METHOD
Market Overview	More than two million patients in Japan
Stage of Development	Compound-screening, in progress

Project Title

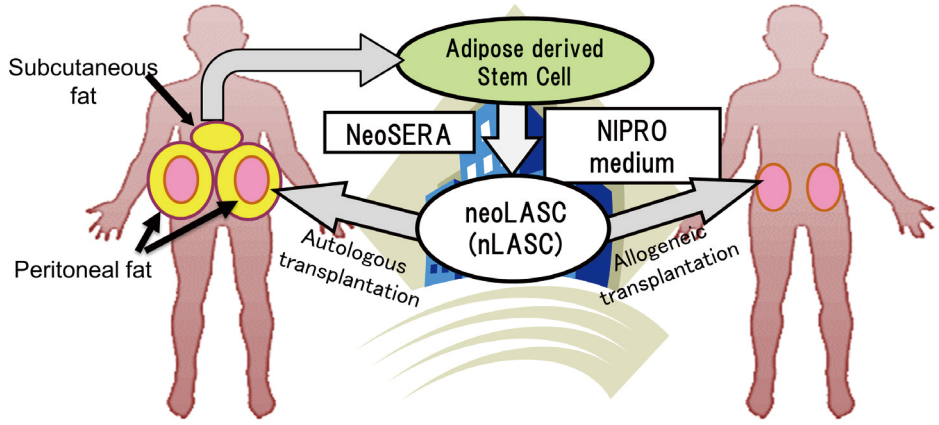
Development of novel culture system of MSC for renal disease

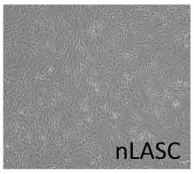
Organization

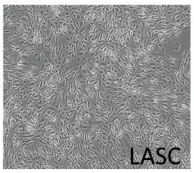
Nagoya University

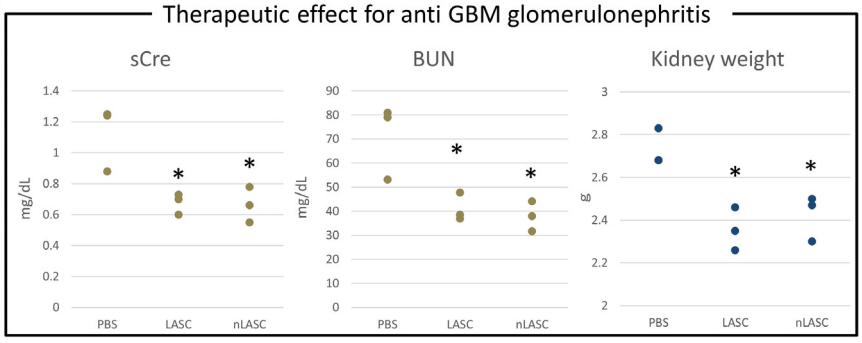
Principal Investigator

Syouichi Maruyama









Target Disease (Applications)	Refractory renal disease IgA nephropathy, ANCA associated glomerulonephritis
Abstract	We have successfully developed a novel and simple method of large scale production of adipose-derived stem cells. These cells or LASC (low serum cultured adipose derived stem cells) show stronger effect of organ regeneration and immune modulation than BM-MSC(bone marrow derived stem cell). In this study, we aim for development of novel xeno free ASC for clinical application in partnership with NIPRO Corp.
Advantages	The treatment using the mesenchymal stem cell is expected to suppress inflammations avoiding infections and it may control end-stage renal disease. The MSC isn't put to practical use as a medicine for kidney.
Patent Information	Cell Preparation Containing Multipotential Stem Cells Originating in Fat Tissue. [WO2008/018450]
Market Overview	IgA nephropathy: 33,000 & ANCA associated glomerulonephritis: 3,000 people in Japan
Stage of Development	Establish the culture methods of nLASC Next stage: Verify the effect of nLASC for refractory renal disease model Final stage: acquisition of utility patent

Project Title

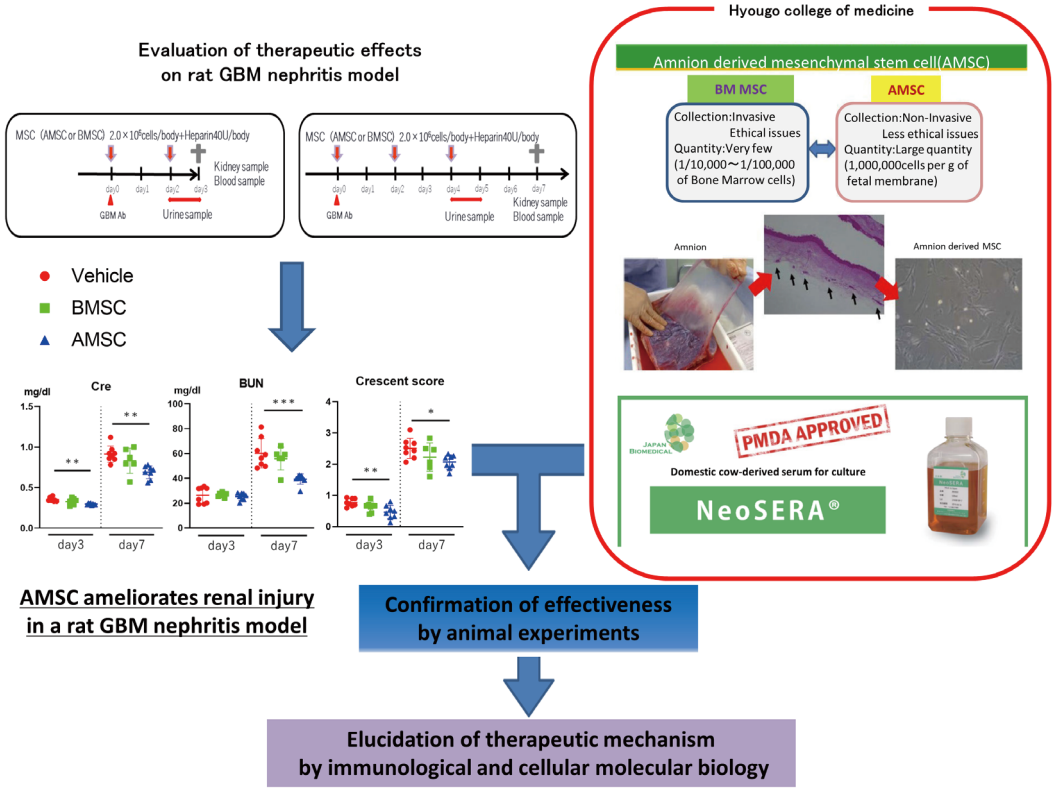
Development of human amnion derived mesenchymal stem cells for the treatment of refractory renal disease

Organization

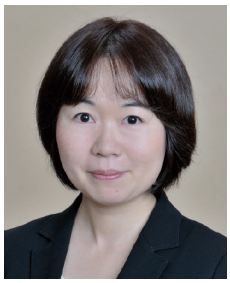
Nagoya University

Principal Investigator

Syouichi Maruyama



Target Disease (Applications)	Refractory renal disease ANCA associated glomerulonephritis
Abstract	The aim is to develop amnion derived mesenchymal stem cells(AMSC) for refractory kidney disease that can be applied clinically. Specifically, the purpose is to obtain a use patent for AMSC cultured in NeoSERA(100% domestic cell culture serum that meets the regulations of the Biomaterials Standard of the Ministry of Health Labor and Welfare).
Advantages	In conventional treatments for ANCA related nephritis, relatively strong immunosuppressive agents have been selected and the development of infectious diseases becomes a problem. Treatment with mesenchymal stem cells is expected to suppress inflammation and end stage renal failure without inducing infection. AMSC using NeoSERA has been started in GVHD and Crohn's disease clinical trial, but its therapeutic effect in kidney disease has not been clarified. Therefore elucidating the mechanism of action of the AMSC on the anti-GBM nephritis model we are using can be said to be an important study subject for the clinical application of the AMSC to renal region.
Patent Information	Considering application for application patent
Market Overview	ANCA associated glomerulonephritis:3000 people in Japan
Stage of Development	The kidney disease model has already been validated, and the animal experiment using the AMSC is in the examination stage. In the future we will investigate the detailed mechanism of action and treatment mechanism in terms of immunological and cellular molecular biology.



Project Title

Development of small-diameter tissue engineered vascular grafts using synthetic elastin and their applications

Organization

Nagoya University

Principal Investigator

Ayae Sugawara-Narutaki

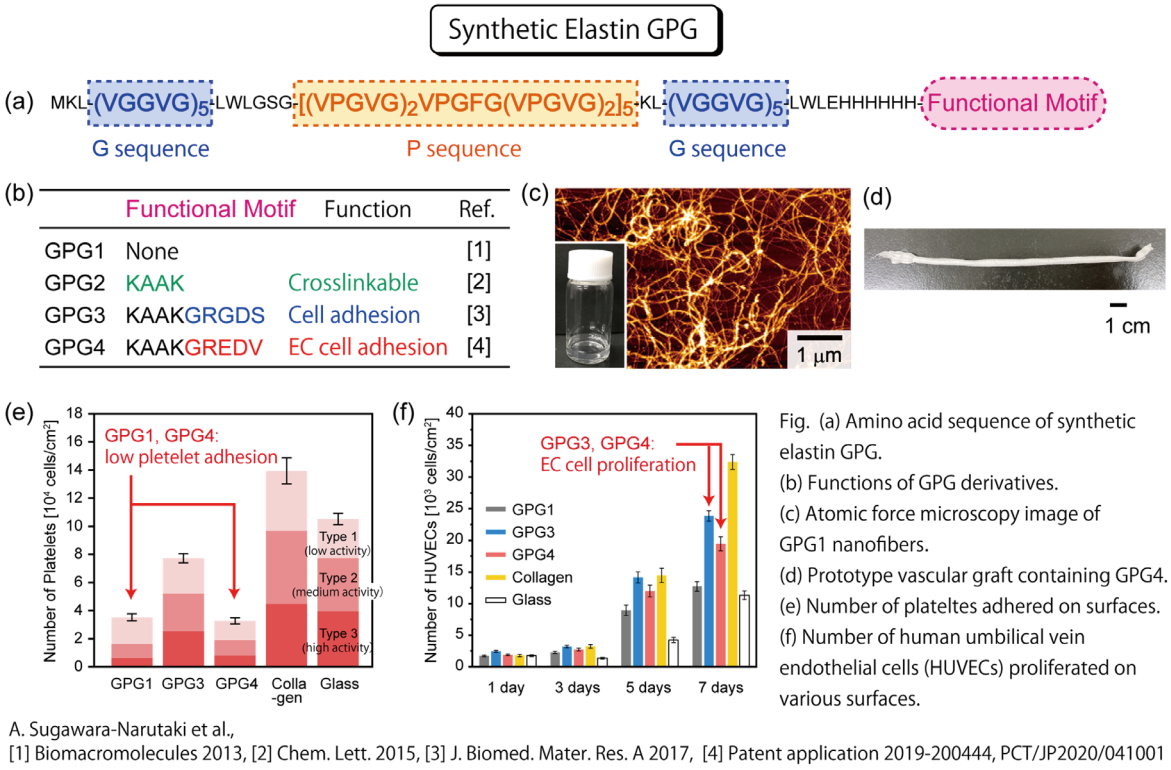


Fig. (a) Amino acid sequence of synthetic elastin GPG.
(b) Functions of GPG derivatives.
(c) Atomic force microscopy image of GPG1 nanofibers.
(d) Prototype vascular graft containing GPG4.
(e) Number of plateltes adhered on surfaces.
(f) Number of human umbilical vein endothelial cells (HUVECs) proliferated on various surfaces.

A. Sugawara-Narutaki et al.,
[1] Biomacromolecules 2013, [2] Chem. Lett. 2015, [3] J. Biomed. Mater. Res. A 2017, [4] Patent application 2019-200444, PCT/JP2020/041001

Target Disease (Applications)	Engineered vascular grafts
Abstract	The objective of this research is to develop small-diameter tissue engineered vascular grafts (TEVG) with an inner diameter of 4 mm or less by using synthetic elastin, which is a recombinant protein. The requirements for small-diameter TEVG include (1) biocompatibility (antithrombotic, non-immunogenic), (2) early endothelialization, (3) mechanical properties equivalent to autologous blood vessels, and (4) appropriate biodegradability. Here we aim to develop synthetic elastin-based TEVG that meet the requirements (3) and (4), since we already obtained proof-of-concepts of (1) and (2).
Advantages	Small-diameter vascular grafts with an inner diameter of 4 mm or less have not been put into practical use due to insufficient patency rate. Elastin, which is a protein constituting the blood vessel wall, is considered to be a promising material for vascular grafts because of its antithrombotic property. However, biological elastin has suffered from its poor processability and lot-to-lot variations. The synthetic elastin has advantages of excellent antithrombotic properties, handleability, and reproducibility, and thus a suitable material for small-diameter TEVG.
Patent Information	Patent Application 2019-200444, PCT/JP2020/041001
Market Overview	Number of patients: 1.7 million in Japan, 170 million in worldwide
Stage of Development	Present: materials property evaluation; Plan: prototype production; Challenges: mass production, non-clinical study

Project Title

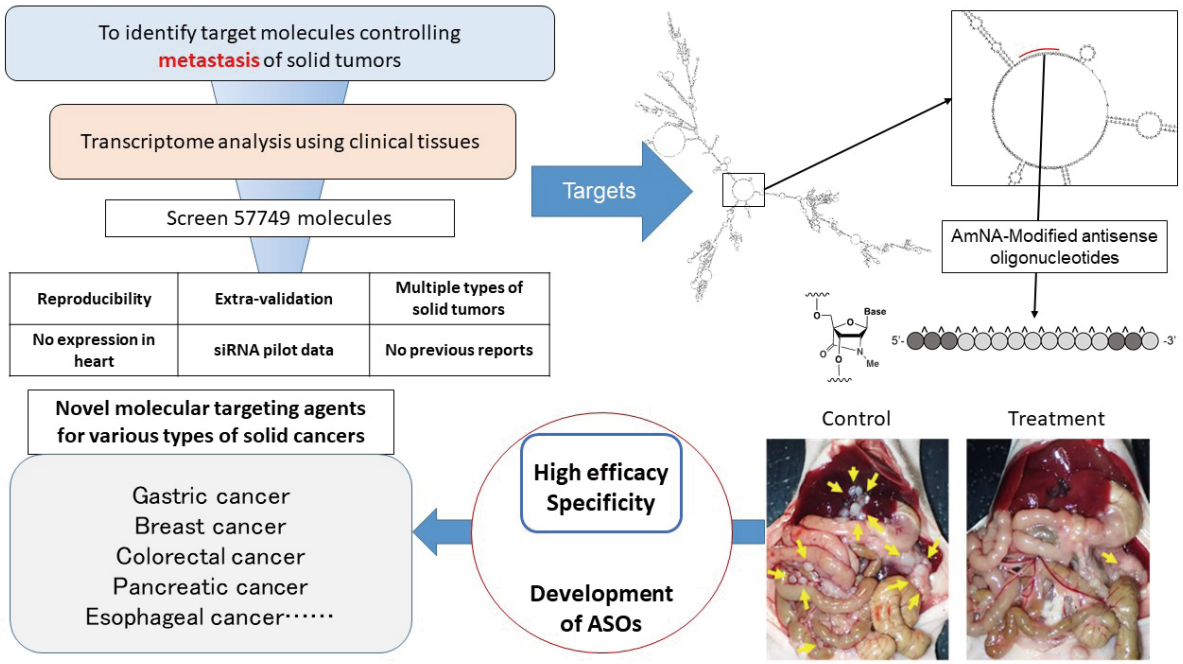
Development of Antisense Oligonucleotides to Treat Gastrointestinal Malignancies

Organization

Nagoya University

Principal Investigator

Mitsuro Kanda



Target Disease (Applications)	Solid tumors
Abstract	Molecules with significantly increased expression in tissues of metastatic or recurrent gastric cancer in the transcriptome analysis conducted to identify new therapeutic target molecules (1) must be validated by external public data such as The Cancer Genome Atlas (TCGA), (2) must be highly expressed in multiple solid tumors, (3) must not have been previously reported in cancer, (4) loss of physiological function must not be assumed to be lethal, and (5) must be safety-conscious. (4) The loss of physiological function is not assumed to be lethal, (5) The expression is not abundant in the central nervous system or heart for safety reasons, and (6) Inhibition of cell proliferation by siRNA knockdown was confirmed in our pilot data. We selected target candidates that met all of the above criteria. We are trying to generate antisense oligonucleotides with excellent inhibitory effects on target molecules and develop innovative nucleic acid drugs for cancer treatment.
Advantages	The target candidate molecules are seeds discovered from clinical specimens of cancers that have shown resistance to treatment, rather than from in vitro cell lines. There have been no reports linking malignant tumors with target candidate molecules, which is highly novel. Since it is different from the target of existing therapeutic agents, it is expected to become a new category of therapeutic agent. We will simultaneously develop companion diagnostic techniques for target selection, which is important in personalized therapy.
Patent Information	Unapplied
Market Overview	Although the prognosis for early radical resection is promising, the prognosis for metastatic and recurrent disease is extremely poor, which is a common and serious problem in all gastrointestinal cancers. Although the lineup of systemic chemotherapy is gradually increasing, mainly with molecularly targeted agents, refractoriness and resistance are limiting the therapeutic outcome, and it is necessary to develop approaches with completely different mechanisms of action.
Stage of Development	Non-clinical proof of concept acquired

Project Title

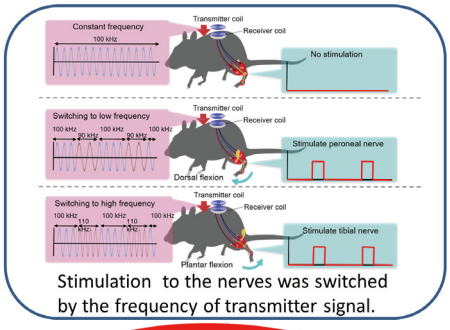
Development of wirelessly powered multi-channel neurostimulator for connecting peripheral nerve with machine

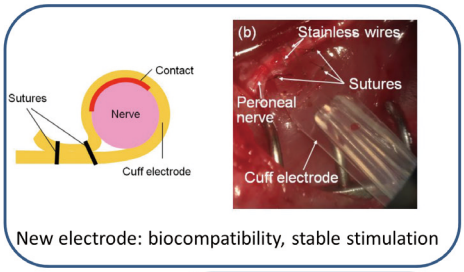
Organization

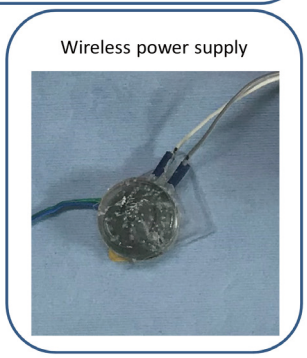
Nagoya University

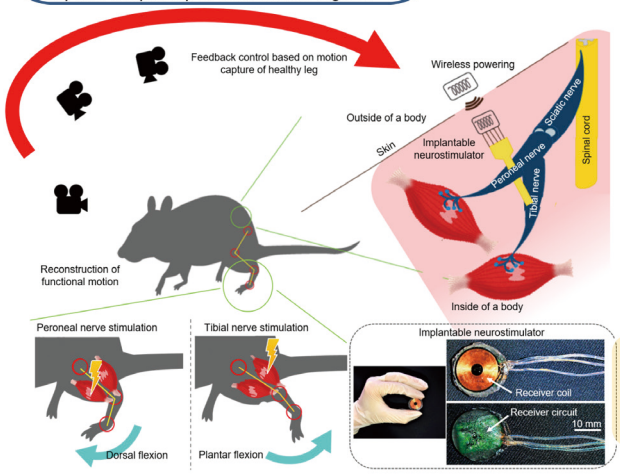
Principal Investigator

Katsuhiro Tokutake









Development of wirelessly powered multi-channel neurostimulator for connecting peripheral nerve with machine

Target Disease (Applications)	Paralysis from upper motor neuron disease (stroke and spinal cord injury)
Abstract	In upper motor neuron diseases, functional electrical stimulation is useful and can move paralyzed muscle by stimulating lower motor neuron. The aim of our study is to develop wirelessly powered multi-channel neurostimulator which can regulate many nerves and joints with high accuracy. We have developed the new neurostimulator as below with Department of Micro-Nano Mechanical Science and Engineering, Nagoya University. 1)electrode: biocompatibility, stable stimulation , 2)Wireless power supply , 3)Regulator system for control many nerve and joint
Advantages	This system can regulate complicated movements with high accuracy. And patients feel comfortable for wireless power supply.
Patent Information	Application number: Japanese Patent Application No. 2020-071547, 2021-168453
Market Overview	Spinal cord injury (domestic: about100,000 cases, US: 230,000-320,000 cases) Stroke (domestic: about 1,200,000 cases, US: 6,800,000 cases)
Stage of Development	We implanted cuff-type electrodes made of a novel silicone material and confirmed that the stability of the stimulation was maintained after implantation in the body. By improving the resolution of the device, we were able to achieve very fine control. In addition, it was possible to control the paralyzed muscles at the appropriate timing by transmitting stimuli from a wireless power source triggered by movements of the healthy forelimb.

Project Title

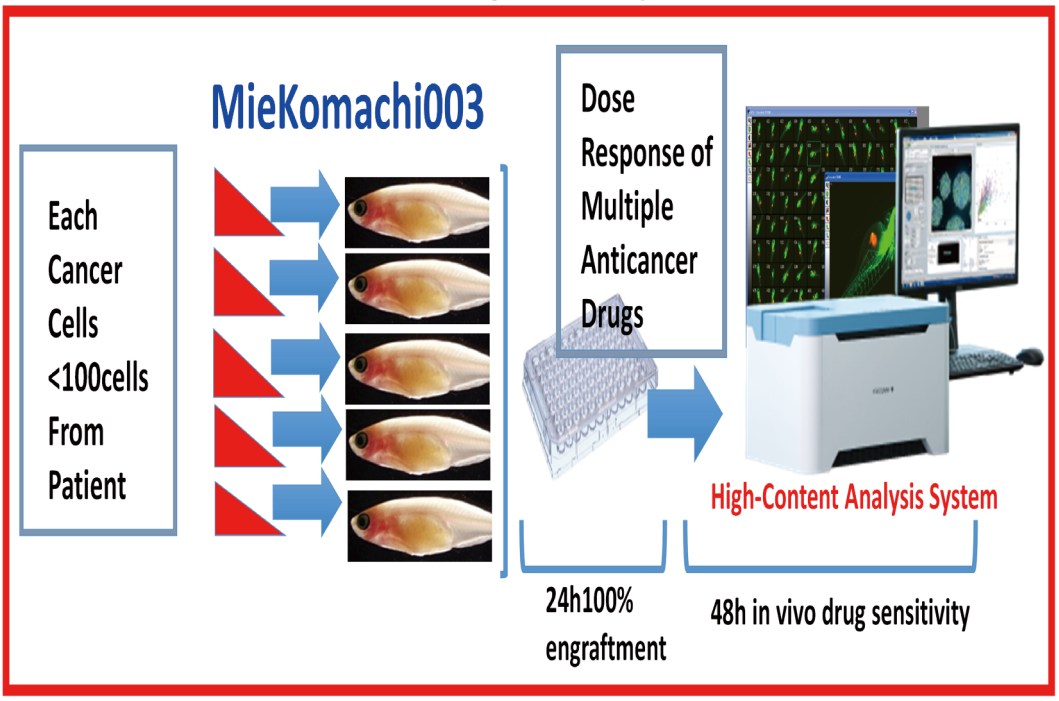
Automated Zebrafish-Based Drug Discovery System for Cancer Precision Medicine

Organization

Mie University

Principal Investigator

Toshio Tanaka



Target Disease (Applications)	Indications are all malignancies and provide improved prognosis for drug therapy and drug discovery.
Abstract	Since the responsiveness prediction of clinical cancer therapeutic agents is 10% or less, cancer cell 2D culture is no longer used. And the patient-derived cancer xenotransplantation model is utilized because the prediction ability of 80% or more. However, it takes about one year for the mouse model(PDXM) to produce results, so the zebrafish model(PDXZ), which produces drug susceptibility test results in one week and optimize anticancer drug treatment, improve prognosis and drug discovery.
Advantages	In patient-derived xenograft zebrafish model (PDXZ), dose-response data of a large number of anticancer agents can be reported within one week. However, since the manual method requires extremely advanced technology, which hinders accuracy, throughput, and widespread use, we will develop an automated system for patient-derived xenograft zebrafish model(PDXZ).
Patent Information	Patent Application2020-175017,Patent5295733,Patent6180134, Patent6329836, EP2201095,US9127245,US10258990,DE602008040454.4,
Market Overview	Number of patients with indications: All cancers 977,393, Japan Current market and future forecast Public information: 8.5 billion yen, 2023 10.5 billion yen forecast
Stage of Development	Currently, we have applied for a basic patent and are strengthening the patent. In the future, we will realize this automatic patient cancer transplant zebrafish model (PDXZ) system and utilize it for next-generation personalized medicine and drug discovery.

Project Title

Development of peptide targeting FGFR2 amplified gastric cancer

Organization

Aichi Cancer Center Research Institute

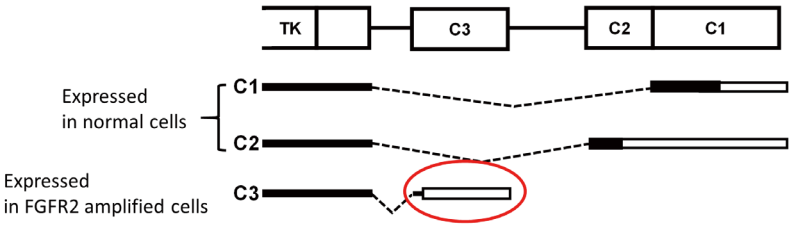
Principal Investigator

Hiromichi Ebi

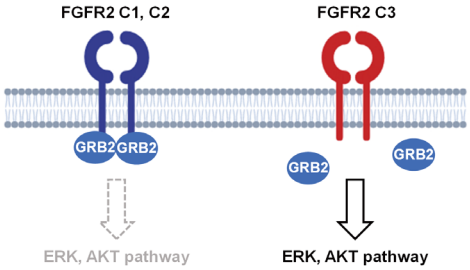
Backgroud

- **Gastric cancer is a major cause of cancer death in Japan.**
- **FGFR2 (fibroblast growth factor receptor 2) amplification is observed in about 10% of gastric cancer.**
- **FGFR tyrosine kinase inhibitor shows limited efficacy due to toxicity and intratumor heterogeneity of gastric cancer**
- **Less toxic therapy targeting FGFR2 amplified gastric cancer is needed.**

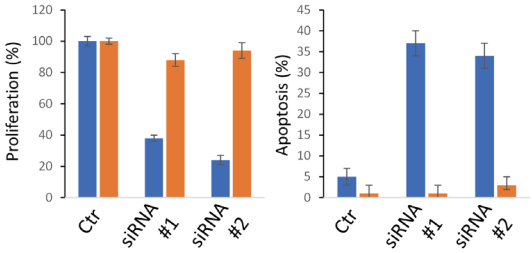
Splice variant specifically expressed in FGFR2 amplified cells



FGFR2 C3 constitutively activates survival signal



siRNA against FGFR2 C3 variant leads to cell death specifically in FGFR2 amplified cells



Target Disease (Applications)	Gastric cancer FGFR2 amplification is observed in about 10% of gastric cancer
Abstract	While 10% of gastric cancer harbor FGFR2 amplification, FGFR tyrosine kinase inhibitor shows limited efficacy because of toxicity and intratumor heterogeneity. The purpose of this project is to develop peptide targeting splice variant specifically expressed in FGFR2 amplified cancer
Advantages	By targeting variant specifically expressed in FGFR2 amplified cancer, the peptide will be less toxic
Patent Information	
Market Overview	The number of death caused by gastric cancer is about 44000 per year
Stage of Development	Obtaining POC in vivo

Project Title

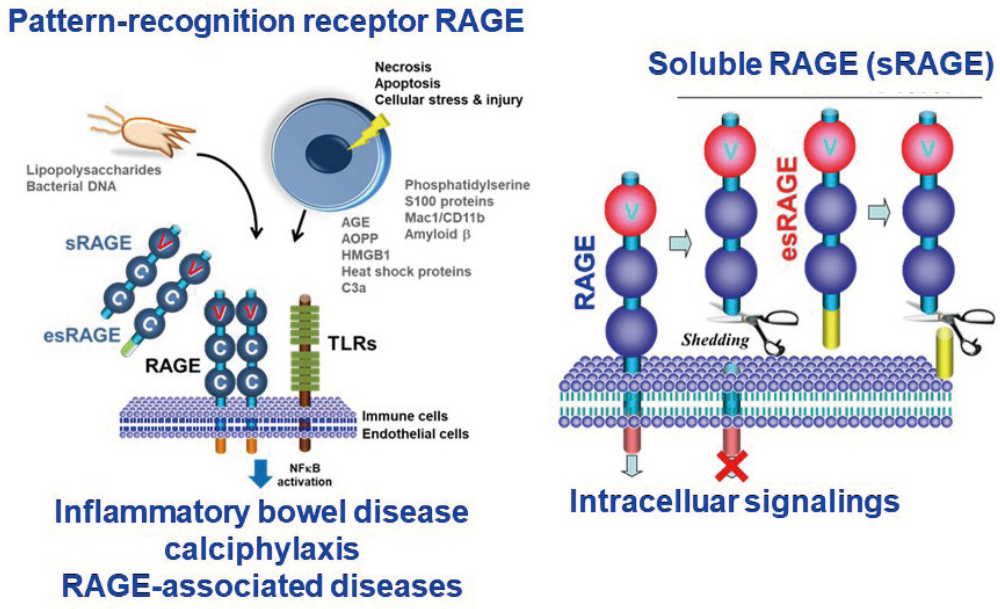
Screening and validation of drugs for converting pattern-recognition receptor RAGE to a soluble decoy form

Organization

Kanazawa University

Principal Investigator

Yasuhiko Yamamoto



Screening and validation of drugs for converting RAGE to a soluble decoy form

Target Disease (Applications)	Inflammatory bowel disease, calciphylaxis, etc
Abstract	Receptor for advanced glycation end-products(RAGE), a transmembrane receptor of the immunoglobulin superfamily and a pattern recognition receptor, reportedly plays an important role in various pathophysiological processes such as inflammatory diseases, diabetic complications, atherosclerosis, cancer, and Alzheimer's disease. Soluble RAGE (sRAGE), generated via proteolytic cleavage of RAGE on the cell surface, function as decoys for RAGE and potentially protect against RAGE-ligand-mediated cytotoxicity. We are performing a drug screening study to identify novel chemical candidates to induce RAGE ectodomain shedding, using a drug and chemical compound libraries. This screening study will offer a promising remedy to prevent and treat RAGE-related diseases including inflammatory bowel disease and calciphylaxis.
Advantages	Advantages in our original methods for drug screening Drug repurposing: an effective strategy of identifying new therapeutic use(s) for old/existing/available drugs.
Patent Information	
Market Overview	Inflammatory bowel disease: 0.17 million (Japan) 5 million (World) Calciphylaxis: 150 (Japan)
Stage of Development	Under validation of potential candidates

Project Title

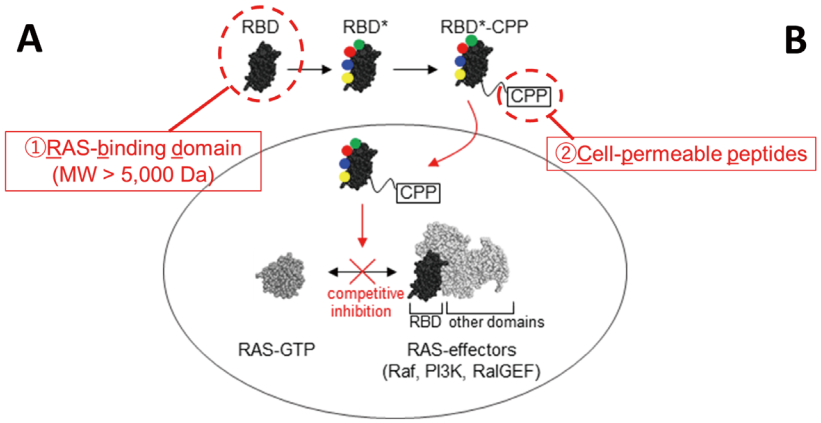
Development of cell-permeable proteins targeting oncogenic RAS

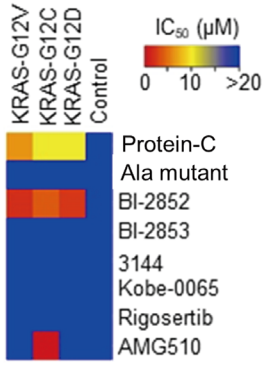
Organization

Gifu University

Principal Investigator

Ryo Honda





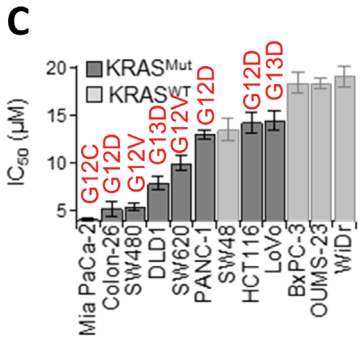


Fig. A: Schematic of our strategy for designing RAS inhibitors. RAS-binding domain (RBD) is delivered into the cytosol by conjugation with cell-permeable peptides (CPP), and competitively inhibits the interaction between RAS-GTP and RAS-effector proteins within the cell.

Fig. B: Comparison of our lead protein (Protein-C) with other RAS inhibitors

Fig. C: The IC_{50} values of cancer cell viability. Protein-C kills all types of Ras-mutated cancer cells.

Target Disease (Applications)	All RAS-mutated cancers
Abstract	Oncogenic Ras proteins, common oncogenic drivers in many human cancers, have been refractory to conventional small-molecule and macromolecule inhibitors due to their intracellular localization and the lack of druggable pockets on their molecular surface. We are developing a novel strategy for designing RAS inhibitors that involves intracellular delivery of Ras-binding protein.
Advantages	Our lead protein crosses the cell membrane via endocytosis, binds to Ras-GTP (Kd = 30 nM), competitively inhibits Ras-effector interaction, and thereby exerts anticancer activity against several KRAS-mutant cancer cell lines in vitro. Moreover, the lead exhibits excellent potency comparable with existing small-molecule pan-RAS inhibitors (IC50 = 10 μM), as well as high target specificity in transcriptome analysis and alanine mutation analysis.
Patent Information	We filed a Japanese patent on August 2020 (ID: 2020-137653).
Market Overview	20 millions patients per year worldwide
Stage of Development	We currently optimize the lead protein using various techniques, such as phage display and liposome encapsulation, to demonstrate the anticancer activity in a xenograft animal model. We believe that collaboration with industry partners is essential for further development, because we are lack of research costs (especially labor costs) and several synthesis technologies.

Project Title

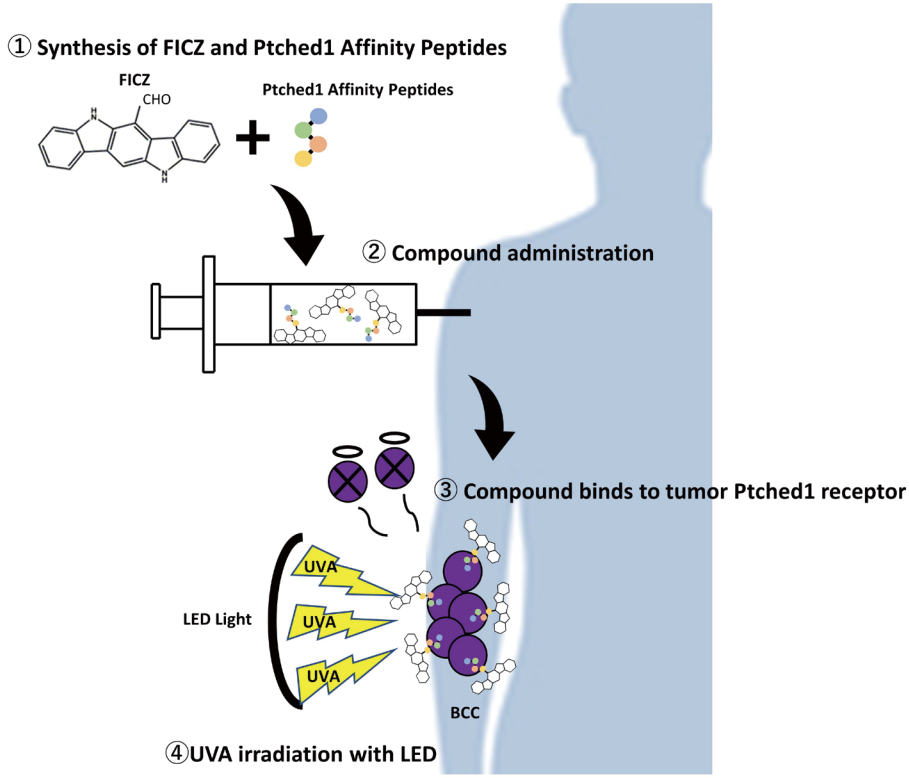
6-formylindolo[3.2-b]carbazole for highly selective photodynamic therapy against basal cell carcinoma

Organization

Nagoya City University

Principal Investigator

Motoki Nakamura



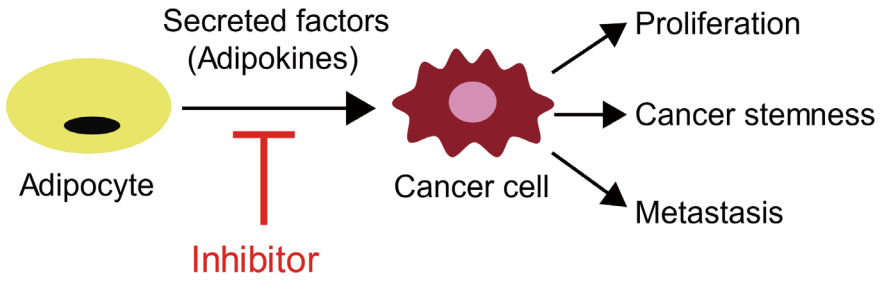
Target Disease (Applications)	Basal Cell Carcinoma
Abstract	Topical application of 5-aminolevulinic acid (5-ALA), a porphyrin precursor, is commonly used in photodynamic therapy (PDT) for skin diseases, we have developed PDT using 6-formylindolo[3,2-b] carbazole (FICZ), which is converted from tryptophan in vivo by UVB, as a new photosensitive substance. FICZ is known to be an endogenous ligand for the Aryl-hydrocarbon receptor (AHR), which binds to and activates the AHR. Since FICZ is metabolized by CYP1A1, which is expressed by the activation of AHR, its UVA phototoxicity is usually not a problem, however, some anticancer drugs such as vemurafenib suppress AHR, resulting in photosensitivity. In this study, we synthesized a substance by joining this FICZ with an affinity peptide for Ptched1, a cell surface receptor of the Hedgehog (Hh) transduction pathway, which is the causative signal of basal cell carcinoma, to enable selective PDT by binding to tumor cells. We prepared two peptides, one modified with FICZ at the N-terminus of the peptide and the other modified with Lys at the C-terminus and its side chain, and confirmed that both peptides are not cytotoxic up to a concentration of 100 μg/ml under non-UVA irradiation and bind to about 70% of basal cell carcinoma cells.
Advantages	Since FICZ is synthesized in vivo and metabolized within a few hours, PDT using the synthetic peptide is expected to be useful as a therapeutic tool with very few side effects.
Patent Information	
Market Overview	Basal cell carcinoma is the most common skin malignancy, accounting for 24% of all skin cancers, with an incidence of 4 per 100,000 per year.
Stage of Development	Current research stage: FICZ synthetic peptide with higher tumor specificity is under development Future research plan: Aiming for corporate matching and clinical trials

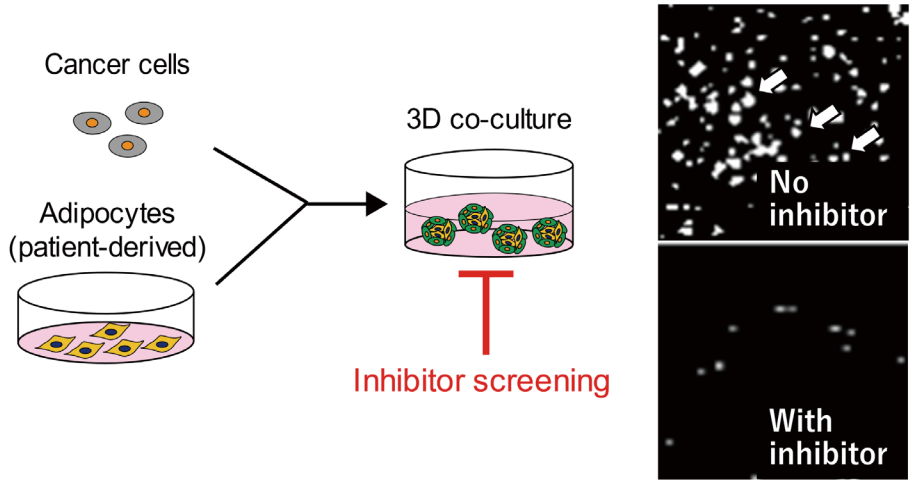
Project Title

Cancer drugs that inhibit adipocyte-derived secreted factors

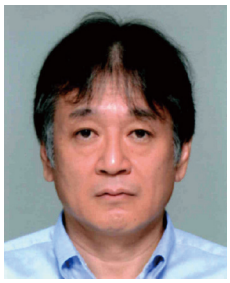
Organization
Fujita Health University

Principal Investigator
Yohei Shimono





Target Disease (Applications)	Breast cancer/Ovarian cancer/Pancreas cancer (Chemotherapeutic drug, metastasis suppressor)
Abstract	Epidemiological studies have confirmed an association between obesity and various types of cancers. We found that the secreted factors of adipocytes promote cancer proliferation and stemness. In this study, using a unique co-culture system of cancer cells and adipocytes, we identified 30 candidate reagents that efficiently inhibit their interaction.
Advantages	No commercially-available chemotherapeutic drugs can target adipocytes. We expect that adipocyte-targeting reagents will be less toxic than currently-available cytotoxic drugs; potentially enabling combination therapies with them.
Patent Information	JP 2019-548758
Market Overview	Breast cancer ~90,000 cases/year, Ovarian cancer ~13,000 cases/year, Pancreas cancer ~40,000 cases/year
Stage of Development	Identification of 30 candidates Preparing for preclinical POC studies



Project Title

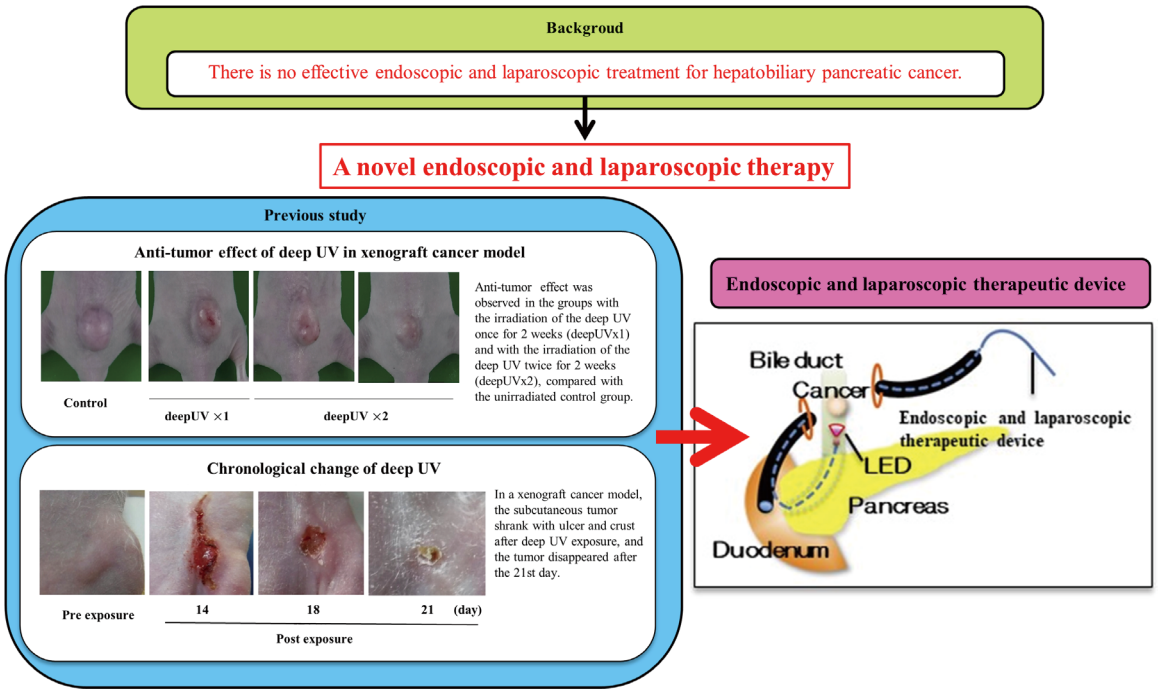
A novel therapeutic device using deep UV for endoscopic and laparoscopic surgery

Organization

Nagoya University

Principal Investigator

Toshio Kokuryo



Target Disease (Applications)	Bile duct cancer, Esophageal cancer, Gastric cancer, Colorectal cancer, Pancreas cancer, Uterus cancer, Bladder cancer
Abstract	There is no effective endoscopic and laparoscopic treatment for hepatobiliary pancreatic cancer. The wavelength range of deep UV (from 250 nm to 350 nm) coincides with the most absorbed wavelength (from 260 to 270 nm) of DNA. As DNA synthesis is inhibited by the DNA mutation, cell death is induced. We aim to enable endoscopic and laparoscopic treatment, and improve the prognosis and QOL of hepatobiliary pancreatic cancer.
Advantages	The efficiency of phototherapy has been clarified as a local treatment for cancer. Since phototherapy acts directly on cancer, it has few complication, such as vomiting. Phototherapy does not require special equipment like radiation therapy. Moreover, our treatment using the deep ultraviolet LED does not require a photosensitizer unlike other phototherapy, and has no side effects such as photosensitivity disease.
Patent Information	Application No : 2019-181220, Date : October 1, 2019
Market Overview	Bile duct cancer : about 20, 000 cases/ year, in Japan DRG reported that the number of bile duct cancer in 2028 will increase by 19% compared to that in 2018.
Stage of Development	Prototype production and improvement Pre-clinical POC acquisition Business tie-up

Project Title

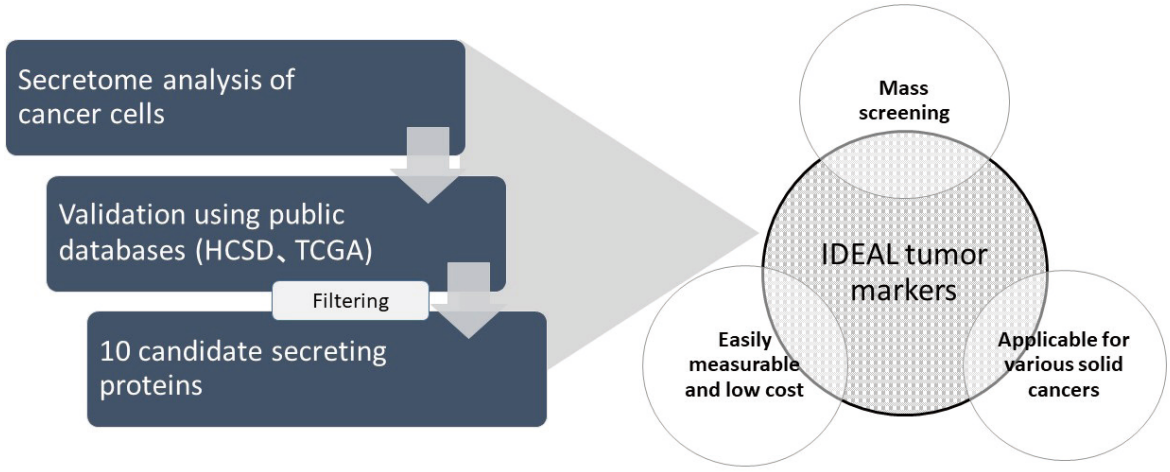
Development of novel serum tumor markers for various types of solid cancers

Organization

Nagoya University

Principal Investigator

Mitsuro Kanda



Target Disease (Applications)	Solid tumors
Abstract	The ideal serum cancer marker is a marker that satisfies the following criteria: it can be screened in a large population of healthy and suspected cancer patients, it is not limited to cancer types or applications, and it can be determined by a versatile measurement method (nucleic acids and methylation are high hurdles for technological development). So far, we have identified candidate markers that satisfy all of these requirements through secretome analysis, which is a comprehensive survey of secreted substances in cancer cells, analysis of public databases (HCSD, TCGA) to ensure the reproducibility and validity of these results, and evaluation of serum values by ELISA on serum samples from healthy subjects and cancer patient populations. The markers were identified. We will obtain monoclonal antibodies with high accuracy and construct our own ELISA kit.
Advantages	1) A completely new serum cancer marker can be proposed. Since it targets a secretory protein whose serum value has not been reported in any solid cancer in the past, its novelty is likely to lead to expansion of patent rights and technology transfer. 2) Most of new biomarker candidates derived from basic research have not been applied clinically. One of the reasons for this is the simplicity of the testing method (nucleic acids and methylation are high hurdles) and the narrowness of the application (target diseases and uses are limited). This development research has overcome this barrier by targeting serum proteins that can be measured by the highly versatile ELISA method, and the roadmap to practical use as in vitro diagnostic products is clear.
Patent Information	Unapplied
Market Overview	For all solid cancers, there is a need for excellent cancer markers that can be measured with serum that can be collected noninvasively and easily, whether for screening in large-scale medical examinations, cancer diagnosis, diagnosis of progression for treatment decisions, determination of treatment efficacy, or monitoring of recurrence after resection.
Stage of Development	Kit development in progress

Project Title

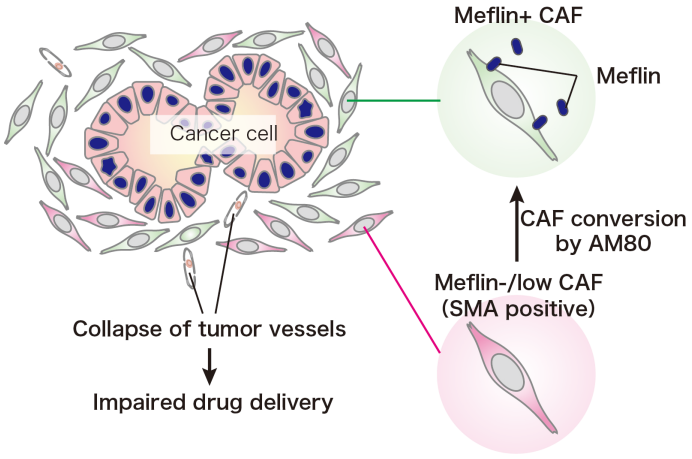
Development of a drug that increases the efficacy of immune checkpoint inhibitors

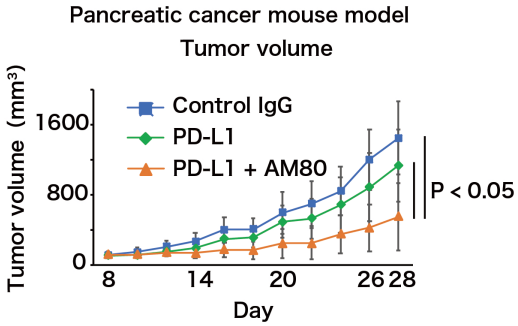
Organization

Nagoya University

Principal Investigator

Atsushi Enomoto





Target Disease (Applications)	Solid cancer accompanied by fibroinflammatory stromal reaction, for which immune checkpoint inhibitors have been approved and used
Abstract	A new therapeutic strategy to improve the efficacy of immune checkpoint inhibitors by inducing changes in the stroma of solid cancer
Advantages	1) Different from other strategies previously reported in terms of mechanisms 2) Can be applied to a wide range of solid cancers
Patent Information	PCT/JP2021/024382
Market Overview	NA
Stage of Development	Preclinical study

Project Title

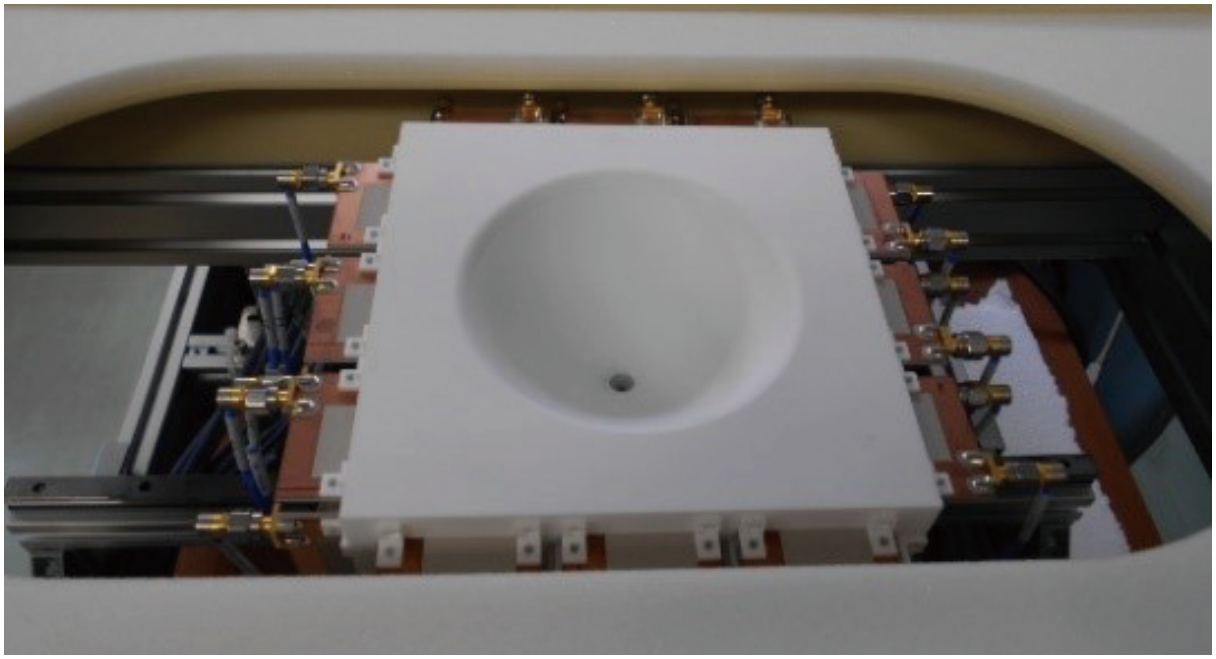
Development of diagnostic imaging equipment using microwave imaging for breast cancer detection

Organization

Aichi Medical University

Principal Investigator

Kimihito Fujii



Target Disease (Applications)	Breast cancer screening, follow-up of chemotherapy / radiation therapy for breast cancer
Abstract	Inverse scattering tomography using microwaves can, in principle, reconstruct the internal structure of living tissue. However, it is difficult to realize due to the large influence of modeling error and noise of the imaging equipment. Therefore, we will try to solve these problems by developing a hybrid image reconstruction method that also uses confocal imaging to identify the position of abnormal parts and an imaging sensor that uses a high-sensitivity antenna.
Advantages	Microwave imaging provides a three-dimensional tomographic image and high contrast prevents cancer from being overlooked in high-density mammary glands. In addition, there is no exposure and there is no pain at the time of examination. Furthermore, no contrast medium is required, the examination time is short, and the diagnostic cost is overwhelmingly low. The price of the device is as low as that of the ultrasonic diagnostic device. The microwave output used is 10 mW (less than 1/100 of the output of a mobile phone), which is safe and enables frequent imaging. The imaging sensor in which multiple high-sensitivity antennas are arranged is an all-electronic type and has no procedure, and it is possible to prevent imaging errors in combination with breast fixation by suction.
Patent Information	Japanese patent number 5605783, 6678985, Japanese patent application number 2018-158617
Market Overview	Annual market size acquired in Japan and overseas: 7.6 billion yen / year The rationale: If half of the domestic X-ray mammography is replaced with 5 years, it will be 10 million × 400 = 4 billion yen / year. In addition, the number of installed units in China and South Korea is about 15,000 and 3,000, respectively, and if 10% of mammography in East Asia is replaced in 5 years, it will be 10 million × 360 = 3.6 billion yen / year.
Stage of Development	Using the proposed hybrid imaging method, we are conducting an imaging evaluation of the phantom. An imaging sensor equipped with a high-sensitivity antenna will be prototyped by September 2022, and clinical imaging is scheduled to begin in October 2022.

Project Title

Research and Development of Scleroderma Treatment with UV-A1 Light Using High Power UV-LED

Organization

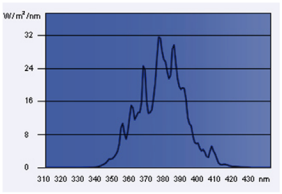
Nagoya City University

Principal Investigator

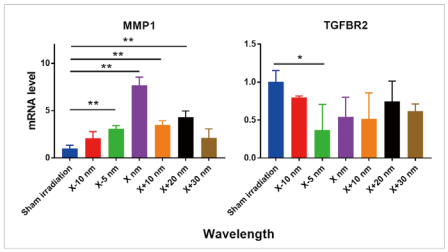
Akimichi Morita

Background

UVA1 phototherapy selectively uses the longer UVA1 wavelengths (340-400 nm), and does not include the shorter UVA2 wavelengths (320-340 nm) or UVB wavelengths (290-320 nm) that cause an erythema reaction. Several studies report the effectiveness of UVA1 phototherapy for various diseases such as atopic dermatitis, T-cell lymphoma, and systemic sclerosis. Since existing equipment is large and consumes a lot of power, it is only used in some countries, including Europe, and has not been approved in Japan. Therefore, we are developing a treatment device that is small and can be used in clinic.



Wavelength characteristics



Development of a medical device

Conventional device　　In development

Based on the results of wavelength characteristics study, we are developing a device to overcome the problems of the conventional device.

Target Disease (Applications)	Atopic dermatitis, Scleroderma and Cutaneous T cell lymphoma
Abstract	UVA1 phototherapy selectively uses the longer UVA1 wavelengths (340-400 nm), and does not include the shorter UVA2 wavelengths (320-340 nm) or UVB wavelengths (290-320 nm) that cause an erythema reaction. Several studies report the effectiveness of UVA1 phototherapy for various diseases. Since existing equipment is large and consumes a lot of power, it is only used in some countries, including Europe, and has not been approved in Japan. Therefore, we are developing a treatment device that is small and can be used in clinic.
Advantages	Small size, Light weight, Hg free
Patent Information	LIGHT THERAPY DEVICE FOR SCLERODERMA, PCT/JP2017/008427
Market Overview	Atopic dermatitis : 450,000, Scleroderma : 20,000 , Cutaneous T cell lymphoma : 10,000
Stage of Development	Current R&D stage: clinical researchUnder clinical research Future research plan: Completion of protocol in existing applicable diseases Outline of the development plan until practical use: Completion of the protocol in May 2022

Project Title

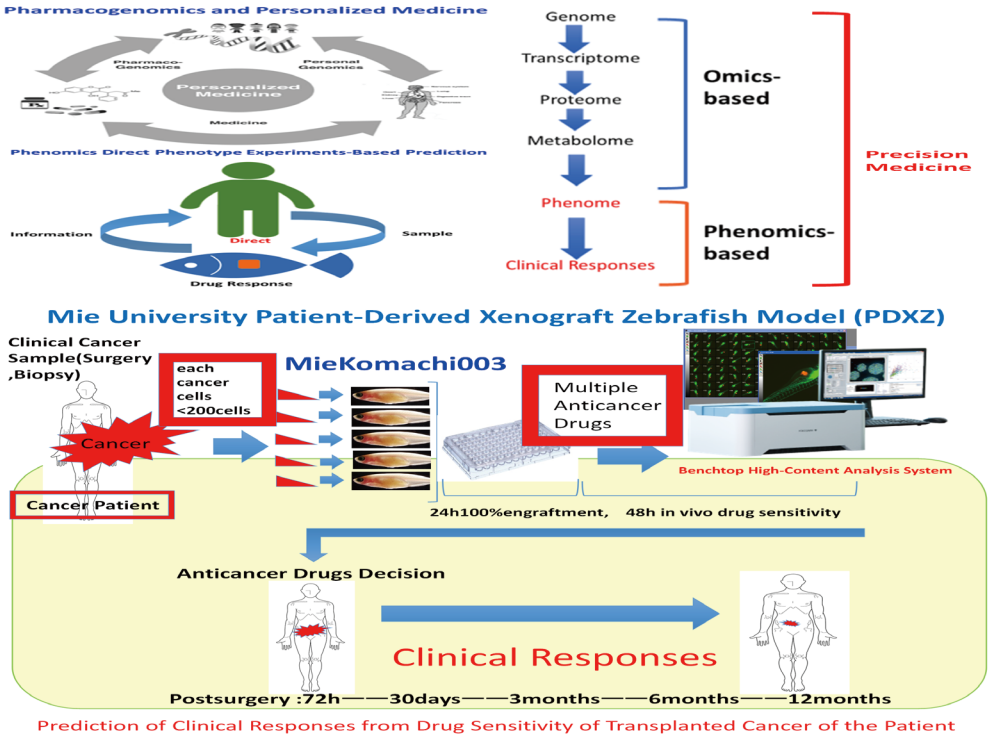
Patient-Derived Xengraft Zebrafish Model(PDXZ) for Companion Diagnostics and Drug Discovery

Organization

Mie University

Principal Investigator

Toshio Tanaka



Target Disease (Applications)	Indications: All malignancies First indications and effects desired for clinical development: All malignancies, improvement of prognosis of drug therapy and drug discovery.
Abstract	Since the responsiveness prediction of clinical cancer therapeutic agents is 10% or less, the cancer cell 2D culture is no longer used. Then patient-derived cancer xenograft model is utilized because of the predictive ability of 80% or more. It takes about a year to get results with mouse model(PDXM), so we developed a zebrafish model (PDXZ)that gives drug susceptibility test results in a week, and optimized anticancer drug treatment, improved prognosis, and developed novel drug discovery screening system.
Advantages	In the case of the patient-derived cancer transplantation mouse model (PDXM), highly immunodeficient mice are indispensable, and more than 100,000 cancer cells are required for the initial transplantation of one mouse, and drug susceptibility testing will be possible one year later. On the other hand, in the patient-derived cancer xenotransplantation zebrafish model (PDXZ), 100 cancer cells per animal are sufficient, and dose-response data of a large number of anticancer agents can be reported within one week. It is transplanted within 36 hours after fertilization, which is immunologically immature, and engrafts in one day. After that, it becomes possible to carry out a therapeutic drug susceptibility test for normal zebrafish including the immune system.
Patent Information	US-10258990, Japanese Patents: 6329836, 6327431, 6384821, 5875010, 6180134
Market Overview	Number of target patients for indications: total cancer 977,393, Japan Current market and future forecast Public information: 8.5 billion yen, 10.5 billion yen forecast 2023
Stage of Development	Obtained a proof of concept for a small number of pancreatic cancer cases. Development and establishment of novel drug discovery screening system with patient-derived xenograft mouse/ zebrafish model(PDXMZ). For future issues, PMDA will be consulted as a companion diagnostic drug development and a development plan will be established.

Project Title

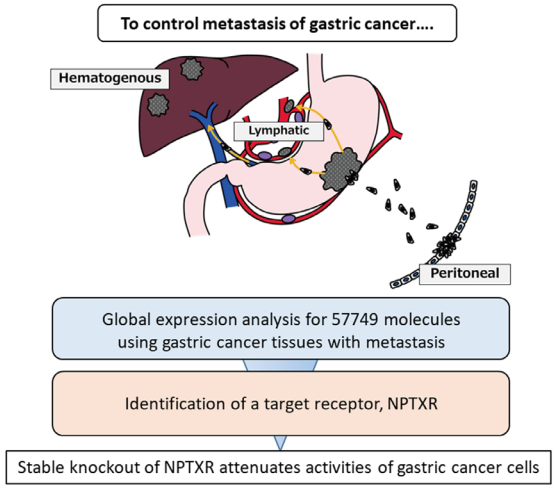
Development of a monoclonal antibody to treat gastric cancer

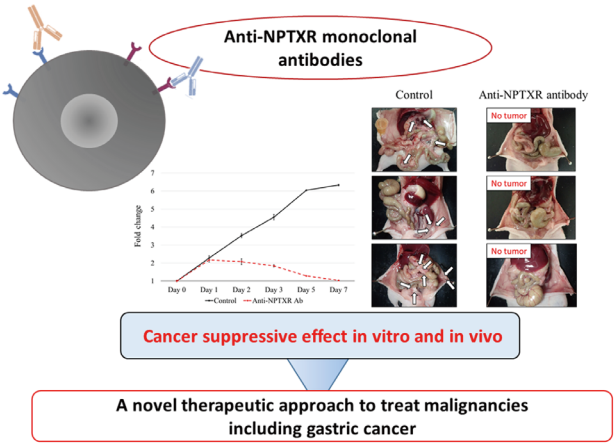
Organization

Nagoya University

Principal Investigator

Mitsuro Kanda





Target Disease (Applications)	Gastric cancer
Abstract	We have developed anti-NPTXR monoclonal antibodies. Humanized anti-NPTXR monoclonal antibodies showed cancer suppressive effect in vitro and in vivo.
Advantages	NPTXR was discovered from patients refractory to the current standard treatment. Thus, those targets can be keys to improve treatment outcomes of advanced gastric cancer. Anti-NPTXR antibody has unique actions and quite different targets from existing molecular-targeting agents mainly acting to receptors of growth factors. Patients expected to have high treatment efficacy can be selected by testing expression of NPTXR (Companion diagnostics). Our tissue microarray data showed overexpression of NPTXR in colorectal cancer, breast cancer, lung cancer, pancreatic cancer and esophageal cancer.
Patent Information	2018-11937,PCT/JP2019/2504 Application: EU, USA, CHINA
Market Overview	Gastric cancer remains the third leading cause of cancer death worldwide with a high mortality rate.
Stage of Development	Under optimization

Project Title

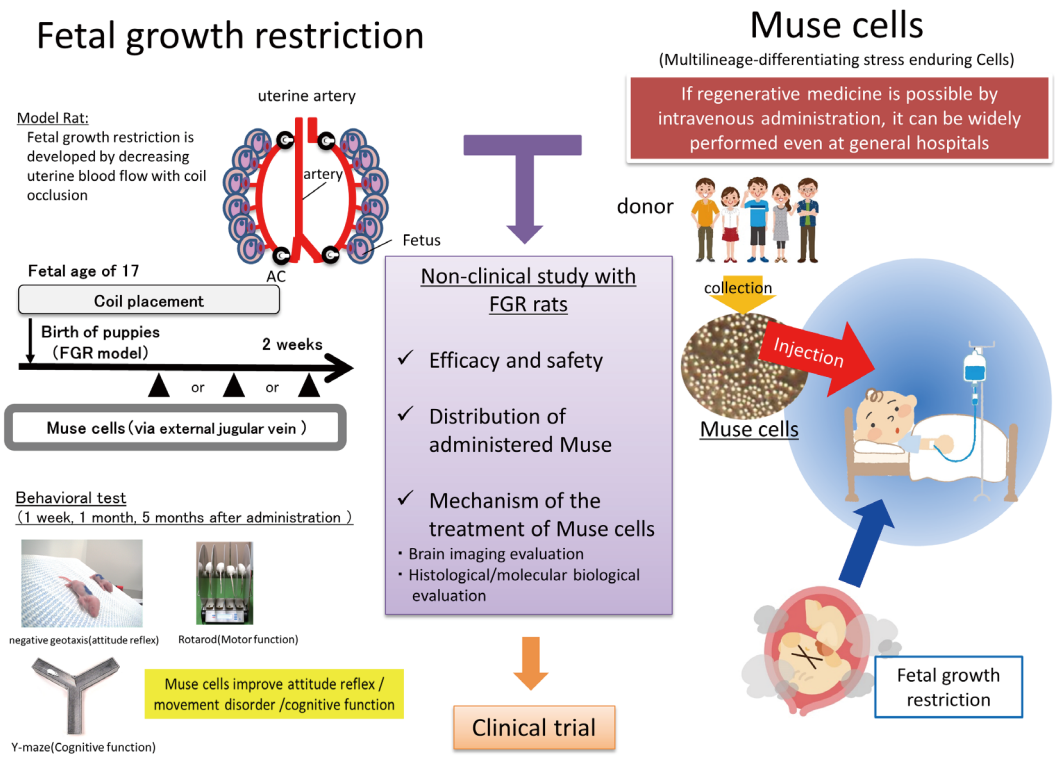
The development of novel therapies using Muse cells for neurodevelopmental disorders in infants with fetal growth restriction

Organization

Nagoya University

Principal Investigator

Masahiro Hayakawa



Target Disease (Applications)	Neurodevelopmental disorders in infants with fetal growth restriction
Abstract	Multilineage-differentiating stress-enduring (Muse) cells are a novel type of endogenous stem cells that can self-renew and display pluripotency. Intravenously injected Muse cells migrate into the injured sites and spontaneously differentiate into functional cells. We have developed FGR model rats and have been evaluating whether Muse cells improve impaired primitive reflex, cognition and movement disorders.
Advantages	There is no treatment at present for neurodevelopmental disorders in infants with fetal growth restriction. In addition, considering the above ideal the characteristic of Muse cells, we can expect an treatment effect. It is advantageous for treating FGR, which has already injured in the uterus.
Patent Information	Filed patent application
Market Overview	FGR is about 8 to 10% of total pregnancy. The prevalence is getting larger due to late childbearing in recent years.
Stage of Development	We established a FGR model rat and have been evaluating the treatment effect of the Muse cells. After that, efficacy and safety assessment of Muse cell product will be performed.

Project Title

Development of novel custom made implants for reconstruction after bone tumor resection

Organization

University of Toyama

Principal Investigator

Taketoshi Yasuda

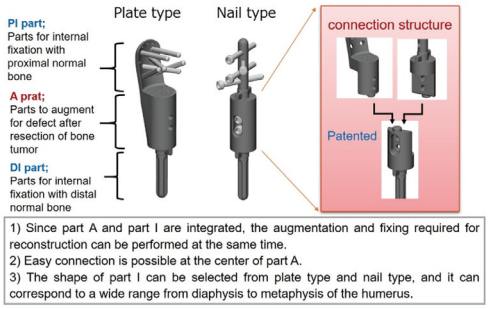


Figure 1. Structure of implant.
The proximal and distal parts are connected in the center to form a single implant.

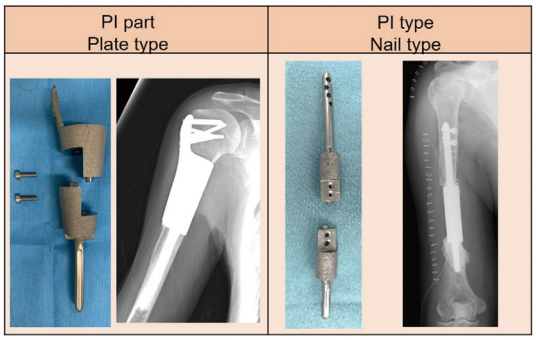


Figure 2. Representative case of humeral implant.

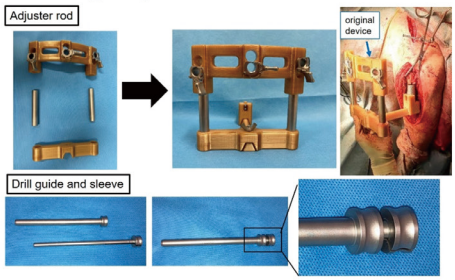


Figure 3. Development of a device for implant placement.
The original devices will allow placement of custom made implants with a small number of reusable devices.

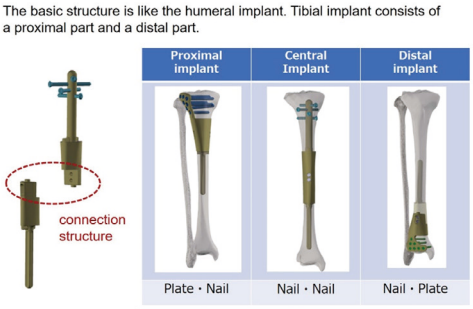


Figure 4. Lineup of tibial implants.
There are three types to accommodate a wide range of tibia.

Target Disease (Applications)	Malignant long bone tumor, cancer (Implant for reconstruction after resection of bone tumor)
Abstract	The purpose of this study is to develop and commercialize the custom made implants be created using electron beam type three-dimensional printer (3D printer) for reconstruction after bone tumor resection.
Advantages	The advantages of this implant are as follow: 1) Preservation of joint function adjacent to the humerus and tibia 2) Structure that can be reconstructed by augmentation fixation at the same and can be easily connected in the center 3) Sufficient strength and permanent biocompatibility 4) Quick supply of products to medical field
Patent Information	Japanese patent publication: No. 2018-33773 Japanese patent publication: No. 2019-25350
Market Overview	Based on epidemiological data in Japan, it is assumed that the number of cases that will benefit when the developed implants is put into practical use is 297 cases / year for humerus implants and 85 cases / year for tibial implants.
Stage of Development	The development stage is the 3rd stage (nonclinical) and the 4th stage (clinical Trials) in parallel. Satisfaction of nonclinical test leads to of nonclinical studies leads to the quick practical application and commercialization.

Project Title

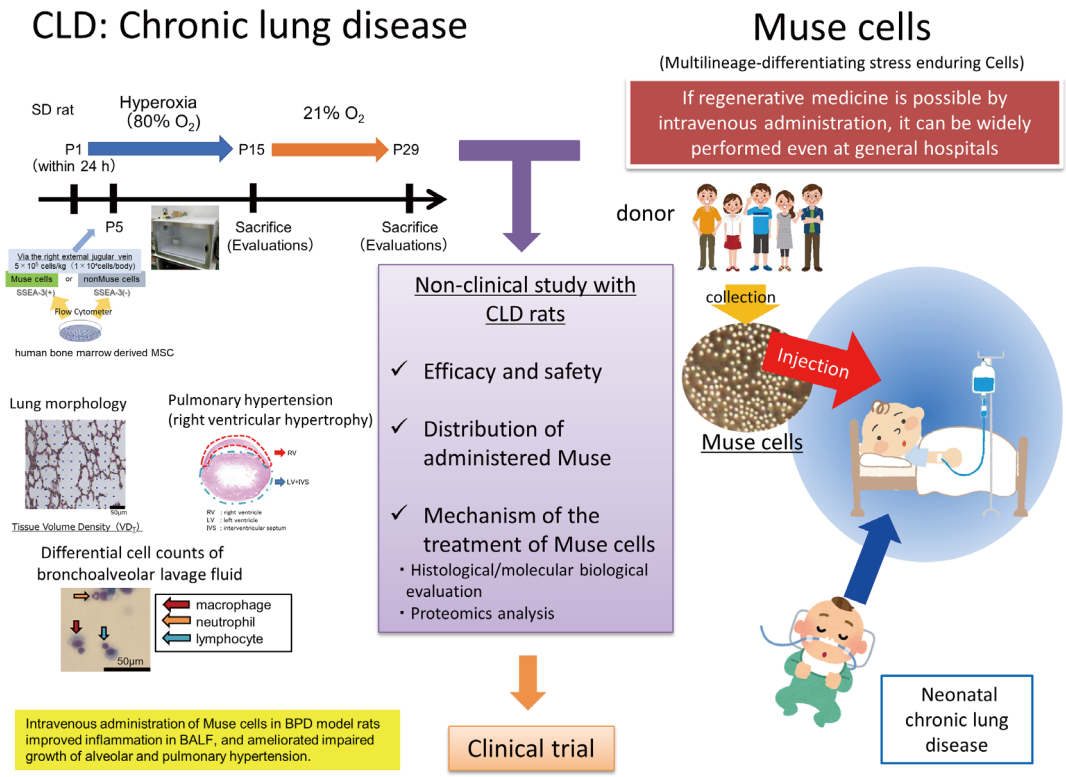
Development of regenerative therapy using pluripotent stem cells (Muse cells) to repair lung injury in neonates

Organization

Nagoya University

Principal Investigator

Yoshiaki Sato



Target Disease (Applications)	Chronic lung disease (CLD)
Abstract	Multilineage-differentiating stress-enduring (Muse) cells are a novel type of endogenous stem cells that can self-renew and display pluripotency. Intravenously injected muse cells migrate into the injured sites and spontaneously differentiate into functional cells. We have been evaluating whether Muse cells improve impaired alveolar growth, and pulmonary hypertension.
Advantages	Muse cells have the potential to self-renew and can differentiate into various types of somatic cells. Moreover, Muse cells readily integrate into injured sites and mediate tissue repair via tissue-specific differentiation.
Patent Information	Filed patent application
Market Overview	The estimated number of patients with severe CLD targeted by this project is 600 neonates per year in Japan. In addition, the social impact is considered to be great.
Stage of Development	We have already shown that 1) intravenously injected Muse cells migrated into injured lung in CLD model rats, 2) Muse cells injected intravenously ameliorated impaired alveolar growth induced by hyperoxia in the rat model, 3) Muse cells, but not non-Muse cells, ameliorated impaired pulmonary hypertension in the CLD model.

Project Title

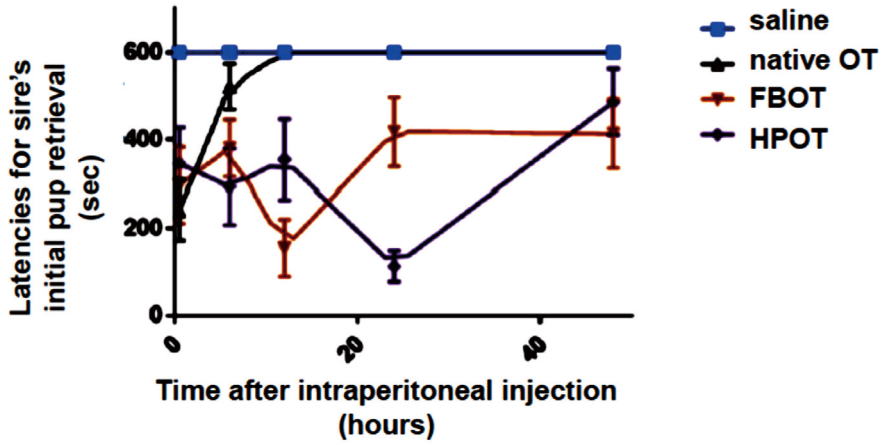
Non-clinical trial of a long-acting oxytocin analogue for the treatment of autism spectrum disorders

Organization

Kanazawa University

Principal Investigator

Shigeru Yokoyama



Prolonged improvement of impaired pup retrieval behavior by autistic model mice. The latencies for pup retrieval by *CD38* gene-knockout sires after a single intraperitoneal injection of saline, native oxytocin (OT), fluorobenzyl OT (FBOT), or hydroxypropyl OT (HPOT). Six hundred seconds means virtually no retrieving; native OT, FBOT and HPOT exhibits significant effects for 6, 16 and more than 24 hours, respectively. (Ichinose et al, J Med Chem. 62: 3297-3310, 2019)

Target Disease (Applications)	Autism spectrum disorders
Abstract	Oxytocin (OT) is a peptide hormone that enhances social communication. Recent clinical trials have reported that intranasal OT administration can improve social communication in autism spectrum disorder (ASD) patients. However, therapeutic potential of OT for ASD is still unsatisfactory, because of its short live in the blood circulation and lower permeability to the brain. To overcome these drawbacks, we have synthesized highly potent OT analogues FBOT (Fluorobenzyl oxytocin) and HPOT (Hydroxypropyl oxytocin; Figure 1).
Advantages	These OT analogues ameliorated social behavioral deficits more effectively and for a remarkably longer time than OT in CD38 gene knockout ASD model mice. FBOT and HPOT may act as long-acting oxytocin mimetics for the treatment of ASD.
Patent Information	Patent pending (Japan): 2018-246141, PCT/JP2019/50089
Market Overview	More than 1% of the general population (1 in 59 children; CDC, 2018)
Stage of Development	To perform a non-clinical test. we are going to establish a method to synthesize a large amount of FBOT, and further characterize its pharmacological properties, including its pharmacodynamics, stability and toxicity, in animal models.

Project Title

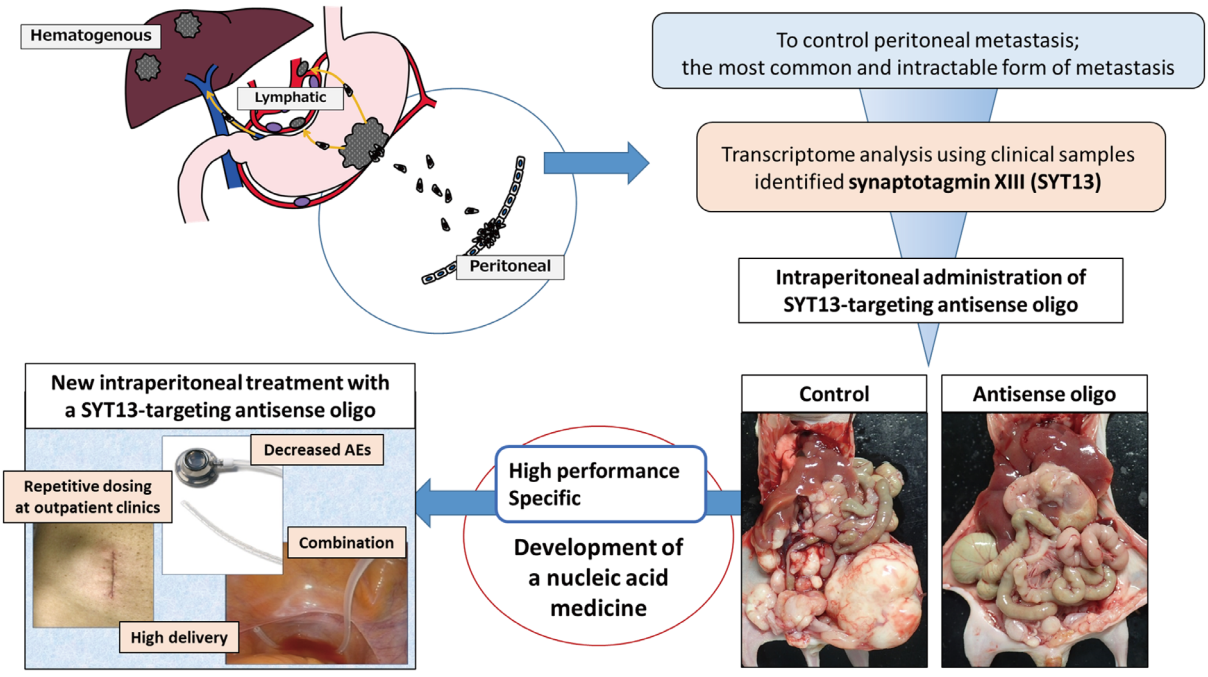
Development of antisense nucleotides specialized for treatment of peritoneal metastasis of gastric cancer

Organization

Nagoya University

Principal Investigator

Mitsuro Kanda



Target Disease (Applications)	Peritoneal dissemination of gastric cancer Intraperitoneal treatment
Abstract	As a result of global expression profiling of 57749 molecules, we successfully detected synaptotagmin 13(SYT13) specifically overexpressed in gastric cancer tissues with peritoneal dissemination. Based on data of treatment efficacy in vivo, toxicity and off-targeting, we conclusively determined the product as ASO-4733.
Advantages	Antisense oligos demonstrating strong inhibitory effect both in vitro and in vivo have been obtained. A companion diagnostic tool is available. SYT13 is a novel target completely different from existing therapeutic antibodies to treat malignancies. SYT13-targeting antisense oligos developed by the National Institute of Biomedical Innovation is transfected into cancer cells without any transfection agents.
Patent Information	2019-154968 PCT/JP2020/32270
Market Overview	Gastric cancer remains the third leading cause of cancer death worldwide with a high mortality rate.
Stage of Development	Preclinical tests (non-clinical toxicity test, safety pharmacology test and non-clinical pharmacokinetic study)

Project Title

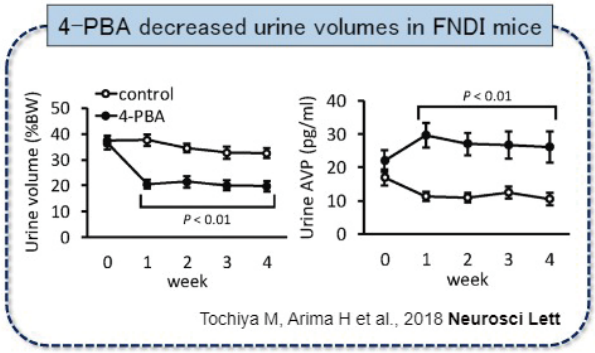
Study of discovery of drugs reducing endoplasmic reticulum stress of familial neurohypophysial diabetes insipidus

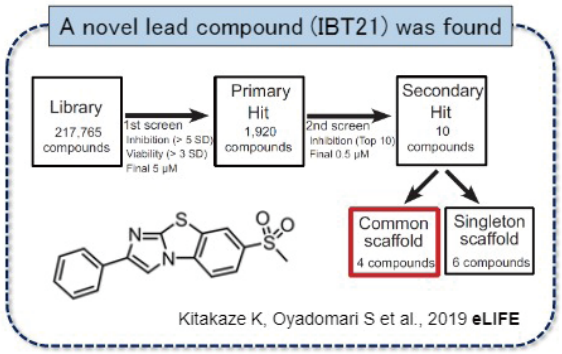
Organization

Nagoya University

Principal Investigator

Hiroshi Arima





- The ER stress reduction will be the first radical therapy for FNDI.
- ER stress has been implicated in the pathogenesis of several diseases such as neurodegenerative diseases. Drugs that reduce ER stress have the potential to be used clinically for the treatment of these diseases.

Target Disease (Applications)	Familial neurohypophysial diabetes insipidus (FNDI)
Abstract	FNDI is an autosomal dominant disorder that manifests itself in early childhood due to a progressive reduction in release of arginine vasopressin (AVP), an antidiuretic hormone. The analyses of FNDI model mice revealed that endoplasmic reticulum (ER) stress has been implicated in the pathogenesis of FNDI. We demonstrated that 4-phenylbutyric acid (4-PBA), which is known to reduce ER stress, increased AVP secretion, and thereby decreased urine volumes in FNDI mice. We have already established the screening system of the ER stress reduction, with which a novel lead compound (IBT21) was found. We further explored a modified compound IBT30, which is more effective than IBT21 in terms of reducing ER stress. In this study, we will examine the reducing effects of IBT30 on ER stress in AVP neurons of FNDI mice.
Advantages	Desmopressin, an existing drug for FNDI, is only a symptomatic treatment, and it is difficult to maintain water balance with this drug. IBT30 developed in this study will be the first fundamental therapeutic drug for FNDI.
Patent Information	Patent Application 2017-255484, PCT/JP2018/47617, WO2019/131656
Market Overview	Familial neurohypophysial diabetes insipidus: 100 ER stress has been implicated in the pathogenesis of several diseases such as neurodegenerative diseases and diabetes mellitus. Drugs that reduce ER stress have the potential to be used clinically for the treatment of these diseases.
Stage of Development	Establishment of a preclinical proof of concept

Project Title

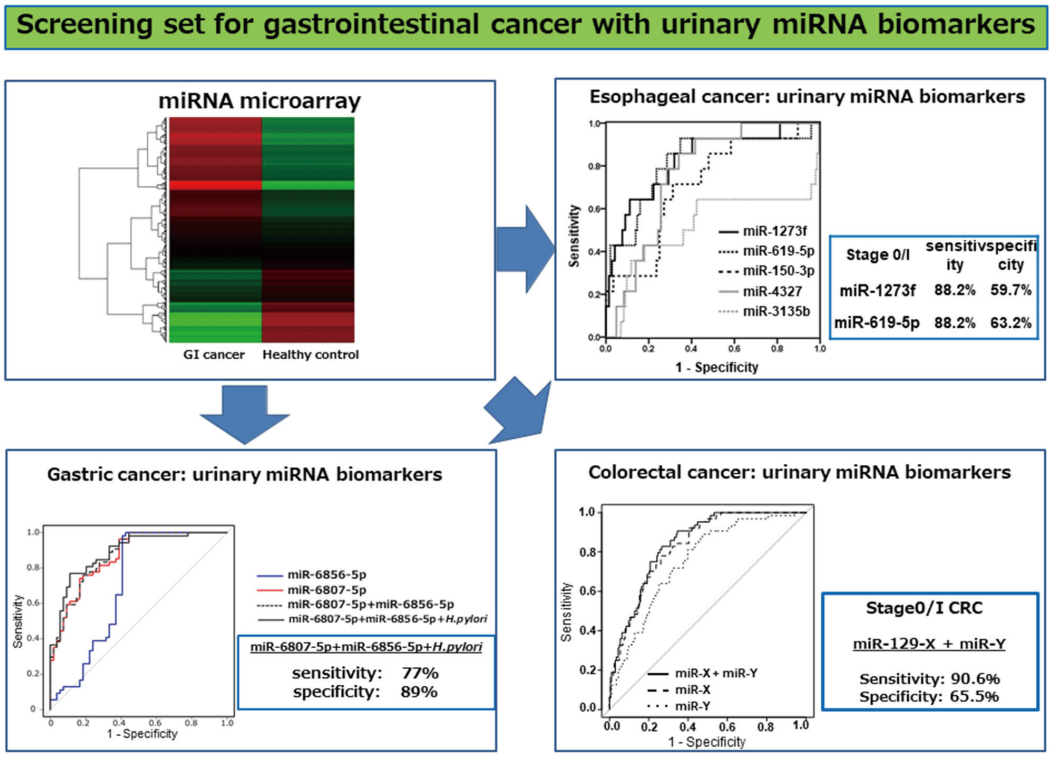
Urinary miRNA biomarker for early detection of gastrointestinal cancer

Organization

Nagoya City University

Principal Investigator

Takaya Shimura



Target Disease (Applications)	Esophageal cancer, Gastric cancer, Colorectal cancer: Gastrointestinal cancer (Non-invasive prediction of the presence of gastrointestinal cancer by analysis of urinary miRNA)
Abstract	Gold standard for diagnosing gastrointestinal cancer (GI cancer) including esophageal cancer (EC), gastric cancer (GC) and colorectal cancer (CRC) is endoscopic examination with biopsy. However, routine endoscopic examination is difficult to apply as a medical check-up for healthy population because of its invasiveness and high cost. Non-invasive biomarkers are thus hopeful for GI cancer surveillance, however no biomarkers have been identified. Urine is completely non-invasive body fluid and it can be collected anytime, anybody and anywhere. The aim of this research is to discover urinary diagnostic miRNA biomarker for GI cancer.
Advantages	Currently used photofluorography is difficult to detect early-stage EC and GC. Although fecal immunochemical test (FIT) has been widely utilized for screening of CRC, sensitivity for early-stage CRC remains low. In addition, handling feces is complicated for examiners. Commonly used serum tumor markers like SCC, CEA and CA19-9 is not recommended for diagnosis of EC, GC and CRC because of their very low sensitivity. Urinary biomarker is completely non-invasive that enables medical check-up at home.
Patent Information	Three international patents for EC, GC and CRC has been applied.
Market Overview	Target is big market because these GI cancers are one of the most common malignancies in the world and objects for this technology is adults over 40 years old who will receive medical check-up.
Stage of Development	Urinary miRNA biomarker panel has been already established for each GI cancer of EC, GC and CRC. We are looking for the collaborating company for this research.

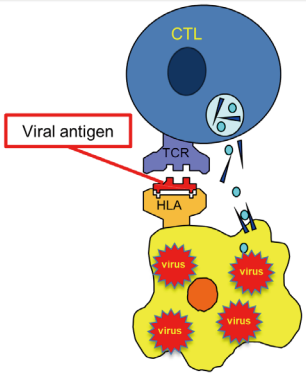
Project Title

Development of Virus Specific Cytotoxic T cells Therapy for Refractory Viral Infection after Allogeneic Hematopoietic Stem Cell Transplantation

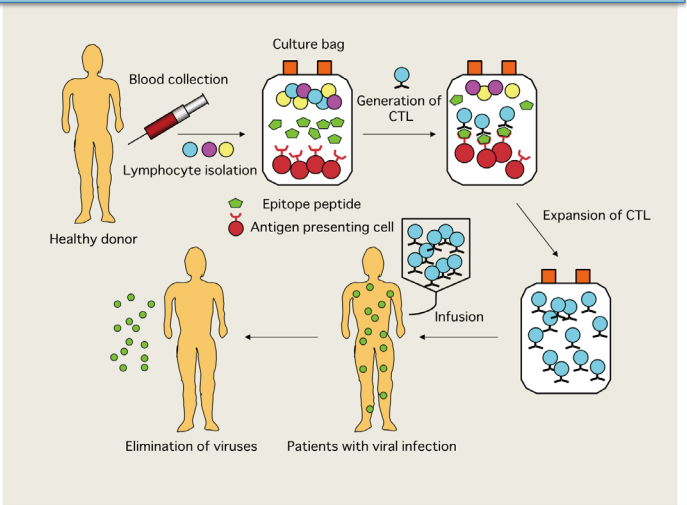
Organization
Nagoya University

Principal Investigator
Yoshiyuki Takahashi

Virus-specific cytotoxic T cells (CTL) recognize viral antigens expressed with HLA on infected cells and kill them.



Generation of virus specific CTL and infusion to the patient



Clinical Study

Phase I study of Third party derived Epstein-Barr virus (EBV) Specific CTL for Refractory Infection after Allogeneic Hematopoietic Stem Cell Transplantation
(jRCTa040190110)

Target Disease (Applications)	Refractory EBV associated Post-transplant Lymphoproliferative Disease (PTLD) after allogeneic hematopoietic stem cell transplantation
Abstract	Production of 3rd party derived virus specific cytotoxic T cells and infusion to the patient
Advantages	eligible to rituximab resistant PTLD "off the shelf" product eligible for unrelated stem cell transplantation
Patent Information	Process patent
Market Overview	30 patients/year in Japan
Stage of Development	Clinical trial

Project Title

Multicenter clinical trial of the Patient-Specific Cardiac Support Device (CSD) with less constraint on Right Ventricle (RV) for Dilated Cardiomyopathy

Organization

Nagoya University

Principal Investigator

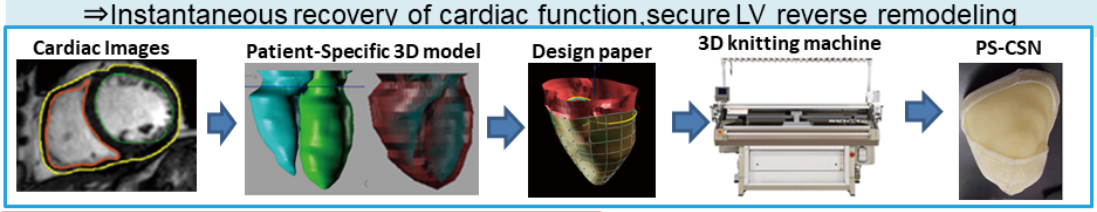
Toshiaki Akita

New Innovative Treatment for advanced Heart Failure:

Patient-Specific Cardiac Support Net (PS-CSN):

- ✓ Personalized designe from CT or MRI images（Patented in US, EU, CN, JP)
- ✓ Less constraint on RV side（Patented in US, CN, JP)

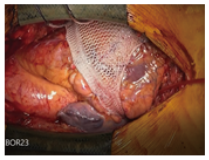
⇒Instantaneous recovery of cardiac function,secure LV reverse remodeling



Sakigake First tract Approval System (2020.Jun)

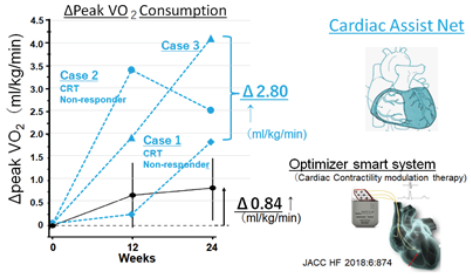
Multi-institutional Clinical trial underway（jRCT s042180025)

PS-CSN



		術前	術後12週	術後24週
Case 1	Peak VO2 (ml/kg/min)	12.5	12.7	14.3
	6MWT(m)	576	630	611
Case 2	Peak VO2 (ml/kg/min)	11.9	15.3	14.4
	6MWT(m)	411	522	555

Benefits: Improvement in Exercise Capacity by Cardiac Assist Net - Comparison with Newly Approved Device for HF Treatment



Target Disease (Applications)	Idiopathic dilated cardiomyopathy (DCM) Secondary cardiomyopathy
Abstract	Multicenter clinical trial is running to evaluate the safety and the usefulness of the Patient-Specific Cardiac Support Device (CSD) with less constraint on RV for Dilated Cardiomyopathy.
Advantages	Patient-specific design→Less invasive and more effective Less constraint on RV→Preserve RV diastolic function and cardiac output Multi-scale & multi-physics cardiac simulation by UT-Heart Inc. → Select the suitable candidate and predict the postoperative cardiac function
Patent Information	Basic patent : registered Method of creating design paper for patient-specific heart correction net: US, EP, CN, JP registered Heart correction net : JP,US, EP, CN registered Registered design : JP(2), CN(1), US(2), EP(1)
Market Overview	Huge market for heart failure (Japan; 1000 cases/year, ¥3.5 billion/year, worldwide >20,000/year $350 million/year) Superior technology to competitor (Mardil: Acorn CorCap successor)
Stage of Development	To establish the safety of this device through small feasibility clinical trial (First in Human study:2019-2021) To establish the efficacy for improvement in cardiac function, cardiac remodeling indices, and QOL through investigator-initiated feasibility clinical trials in 2022, pivotal study in 2023.

Project Title

Alternative treatment of combined physical therapy for postoperative lymphedema

Organization

Nagoya University

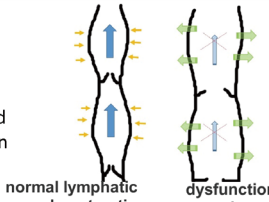
Principal Investigator

Hitoshi Hirata・Katsuyuki Iwatsuki

Early diagnosis and novel treatment for lymphedema

Lymphatic vessels
Part of circular system

Immune reaction, maintenance of body fluid and macromolecule balance, lipid absorption

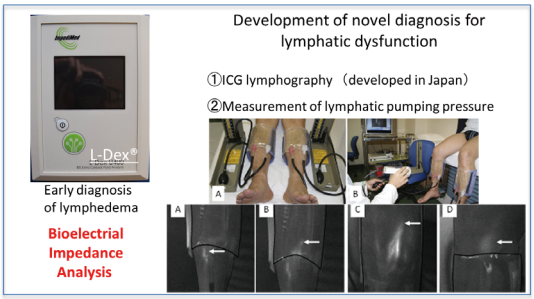


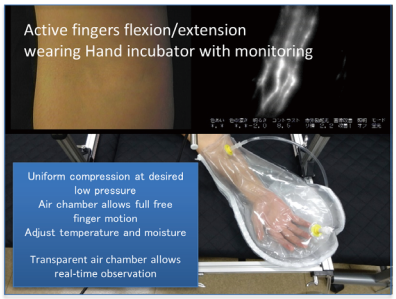
normal lymphatic vessel contraction

dysfunction lymphatic vessel causes lymphedema

Problems of lymphedema
Pathology?
Diagnostic criteria?
Etiology?
Once progressive, Hard to treat

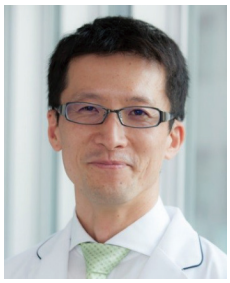
Recent reports : Lymphatic dysfunction → lymphedema
Treatment of lymphedema ※ proper evaluation & intervention





With monitoring of lymphatic function, active motion exercise under low pressure can promote lymphatic flow safely. We will establish a novel treatment algorithm for the subclinical lymphedema.

Target Disease (Applications)	Lymphedema
Abstract	Lymphedema is a potential side effect of cancer surgery, especially in breast cancer and uterine cancer. Once lymphedema is developed, it can be difficult to treat. Based on the evaluation of the lymphatic system in early stage of each patient, we will establish a novel treatment algorithm for the lymphedema.
Advantages	The standard thrapy for postoperative lymphedema is complex physical therapy, which is covered by health insurance in Japan. However, the patients should be continued for the rest of their life and should be performed at a medical institution. The advantage of the medical equipment we are developing is that it can be used at home and can be used easily by themself.
Patent Information	PCT/JP2007/067078, WO2008/044400
Market Overview	Breast cancer (about 80 thousands/year) patients are increased recently in Japan. There are about 100-150 thousands patients with lymphedema in Japan, and about 6000 new lymphedema patients are increased annually. Worldwide, about 1.38 million women are diagnosed with breast cancer per year.
Stage of Development	Now recruiting clinical study for expand indication.



Project Title

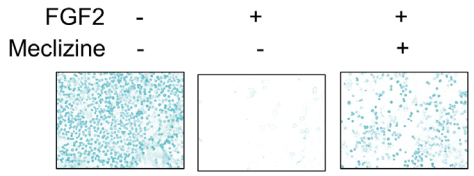
Research and development for the medical treatment of achondroplasia by attenuating FGFR3 signaling

Organization

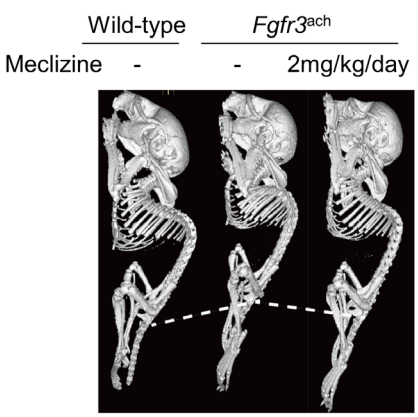
Nagoya University

Principal Investigator

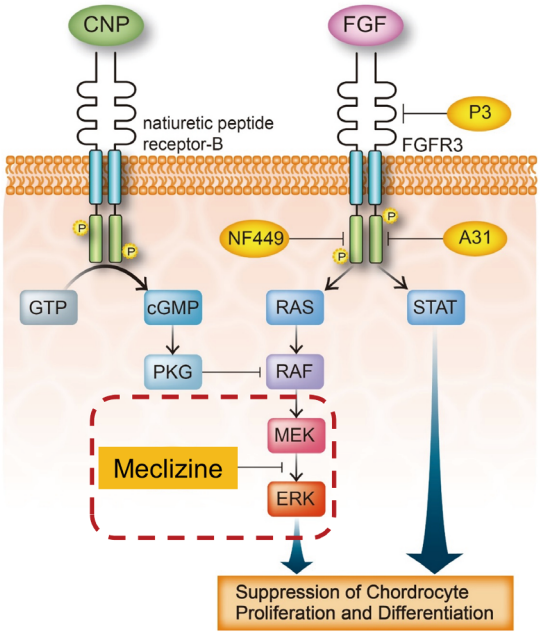
Masaki Matsushita



FGF2 inhibited cell proliferation in rat chondrosarcoma (RCS). Meclizine rescued RCS proliferation.



Oral administration of meclizine for 10 days to mutant mice (*Fgfr3*^{ach} mice) aged 7 day.



Meclizine attenuated ERK phosphorylation in FGFR3 signaling.

Completion of physician-initiated phase 1 clinical trial (12 child patients with achondroplasia).

Target Disease (Applications)	FGFR3-related skeletal dysplasias (achondroplasia, hypochondroplasia, thanatophoric dysplasia)
Abstract	FGFR3 is a negative regulator of longitudinal bone growth and over-activation of FGFR3 causes several short-limbed skeletal dysplasias. By FDA-approved drug screening, we identified that meclizine, an anti-histamine OTC drug, ameliorated abnormally activated FGFR3 signaling in vitro. Meclizine significantly increased the body length in a mouse model of achondroplasia. The plasma concentration of meclizine during treatment was within the range that has been used in clinical settings. We examine potential clinical feasibility of meclizine for the improvement of short stature in FGFR3-related disorders.
Advantages	Meclizine inhibited FGFR3 signaling. Compliance is expected for children due to the oral administration. Economic benefit for developing the treatment of intractable disease by using cheap drug.
Patent Information	Utility patent
Market Overview	1,000 in Japan, 60,000 in worldwide
Stage of Development	Single dose Phase1a clinical trial was completed. Repeated dose Phase 1b clinical trial was completed. Repeated dose Phase 2 clinical trial is in preparation. Juvenile animals test was completed. Long-term toxicity test using animals are ongoing. We are analyzing detail mechanism of meclizine.

Project Title

Phase I study of piggyBac transposon mediated chimeric antigen receptor gene modified T cells for CD19 positive acute lymphoblastic leukemia

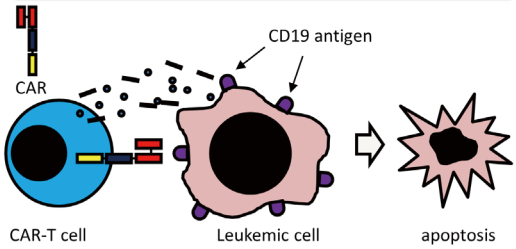
Organization
Nagoya University

Principal Investigator
Yoshiyuki Takahashi

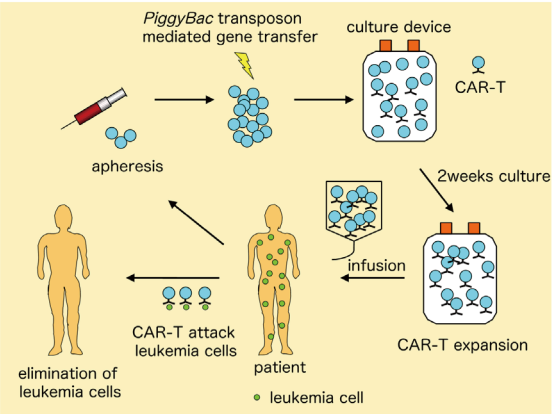
CAR-T Therapy*

* CAR(chimeric antigen receptor)-T cell therapy

CAR-T cells recognize CD19 antigens on leukemic cells and kill them.



Production of CAR-T and infusion to the patient



Clinical Trial (autologous CAR-T therapy)

Phase I study of *piggyBac* transposon mediated chimeric antigen receptor gene modified T cells for CD19 positive acute lymphoblastic leukemia (jRCTa040190099)

Phase I/II study of *piggyBac* transposon mediated chimeric antigen receptor gene modified T cells for CD19 positive malignant lymphoma

Target Disease (Applications)	CD19 positive acute lymphoblastic leukemia, CD19 positive malignant lymphoma, chronic lymphocytic leukemia
Abstract	Production of autologous CD19 CAR-T cells and infusion back to the patient
Advantages	PiggyBac transposon mediated gene transfer (non-viral gene transfer) Reduced cost
Patent Information	Process patent
Market Overview	Acute lymphoblastic leukemia: 1,000 patients/year in Japan Malignant lymphoma: 10,000 patients/year in Japan Chronic lymphocytic leukemia: 2,000 patients/year in Japan
Stage of Development	Acute lymphoblastic leukemia: Clinical trial, sponsor initiated clinical trial Malignant lymphoma: investigator initiated clinical trial

Project Title

Clinical study to evaluate the safety of co-injection of adipose-derived MSC and cord blood hematopoietic stem cells into the bone marrow cavity

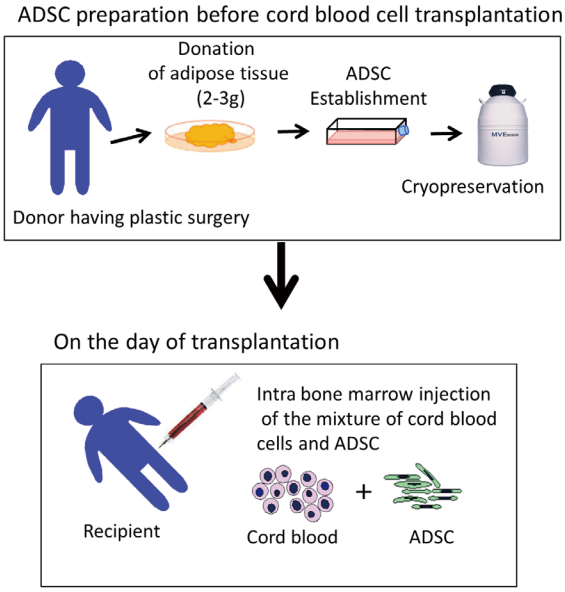
Organization

Aichi Medical University

Principal Investigator

Takayuki Nakayama

Schematic presentation of phase I clinical study to support hematopoiesis with adipose-derived mesenchymal stromal cells (ADSC) in the setting of cord blood transplantation



Adipose-derived mesenchymal stromal cells possess higher hematopoietic-supportive abilities compared to conventional bone marrow derived stromal cells which establish the hematopoietic microenvironment in the bone marrow.

Target Disease (Applications)	Patients who will have cord blood transplantation to treat hematological disorders such as leukemia
Abstract	Engraftment failure will be prevented by intra-bone marrow injection of adipose-derived mesenchymal stromal cells with higher hematopoietic supportive abilities in the setting of cord blood cell transplantation.
Advantages	No other treatment to promote the engraftment of cord blood cells has not been invented yet.
Patent Information	Adipose-derived mesenchymal stromal cells as support medium for cord blood cells Patent Number : Tokugan 2017-162233
Market Overview	Over 1000 patients per a year have cord blood transplantation in Japan.
Stage of Development	Phase I clinical trial is ongoing.

Project Title

A multi-center, single-arm clinical study of the efficacy and safety of rituximab in CIDP patients with IgG4 autoantibodies

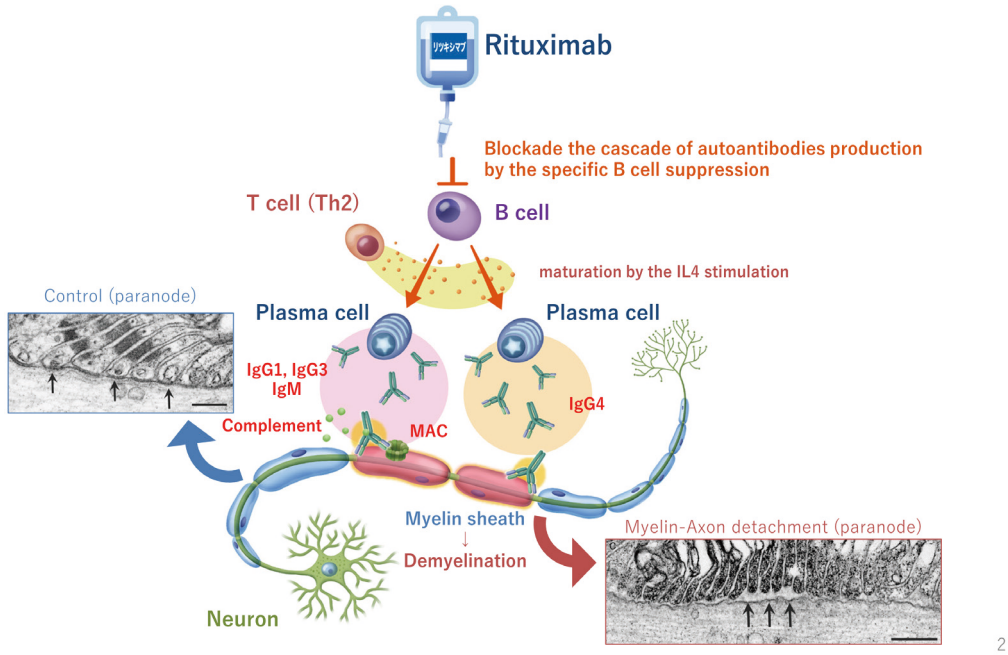
Organization

Nagoya University

Principal Investigator

Masahiro Iijima

Rituximab can exert its therapeutic effect by selective intervention to the B cell-derived pathogenesis of refractory CIDP including IgG4 autoantibodies



2

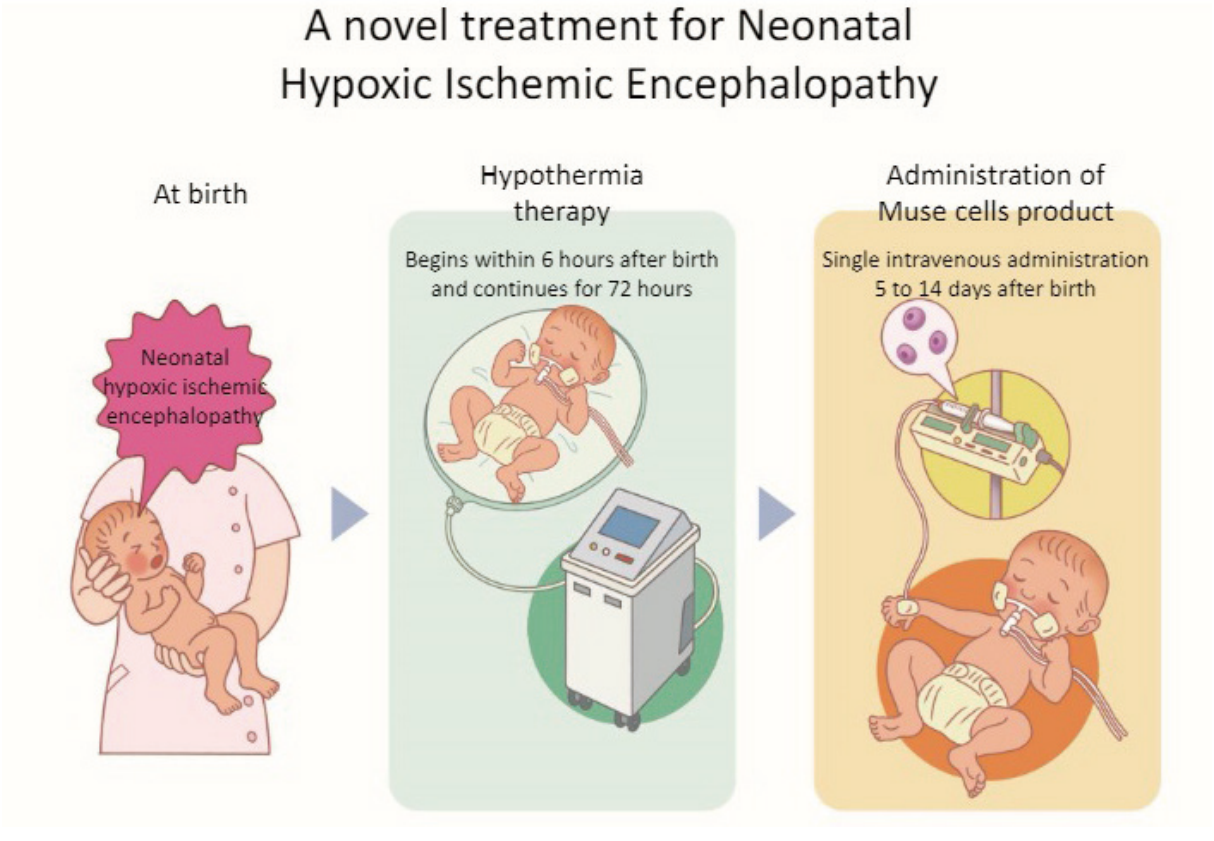
Target Disease (Applications)	CIDP (chronic inflammatory demyelinating polyneuropathy) (The expected efficacy is an improvement of motor dysfunction in refractory CIDP, especially with IgG4 subclass autoantibodies.)
Abstract	A certain percentage of patients with CIDP are positive for autoantibodies belonging to the IgG4 subclass and show resistance to conventional therapies. On the other hand, rituximab strongly suppresses antibody production through B cell inhibition. It is a fundamental strategy for refractory CIDP with known or unknown autoantibodies. Therefore, we plan the investigator-initiated clinical trial (the RECIPE trial).
Advantages	Among conventional therapies (steroid, intravenous immunoglobulins (IVIg), plasmapheresis), IVIg is used as the first-line. On the other hand, IVIg is ineffective for patients with IgG4 autoantibodies, and the others are less effective. Rituximab is a molecular targeting therapy and selectively inhibits antibodies. This is the first trial to verify the efficacy of rituximab for refractory CIDP. Note that IgG4 is a specific subclass lacking complement binding ability, and rituximab is an ideal drug to eliminate the etiology of refractory CIDP involved in autoantibodies.
Patent Information	None
Market Overview	CIDP is one of the designated intractable diseases in Japan, and the number of people with a specified medical expense (specified refractory disease) beneficiary certificate is 4,315 (as of 2008). Of these, IgG4 autoantibody positive cases account for around 10%. Other unknown autoantibodies are also assumed to be involved, but the specific number of patients is unknown. CIDP is mainly treated with IVIg, and refractory cases are treated with progression control therapy that requires intermittent administration for at least one year. Rituximab is expected to be a promising treatment for refractory CIDP since it can be completed in four weekly doses and is expected to be effective over a long period. In contrast, conservative therapeutics such as continuous IVIg maintenance therapy are costly.
Stage of Development	As an exploratory clinical trial, the inclusion of clinical trial participants started in the first quarter of 2019 and was closed in June 2020. We completed the evaluation of all patients in June 2021. During the evaluation period, we had never experienced severe safety episodes. After completing the exploratory clinical trial with a summary report, we will progress early approval or transition to further confirmatory clinical trial.

Project Title

Development a novel regenerative treatment for perinatal brain injury with Muse cells - Exploratory investigator-initiated clinical trial -

Organization
Nagoya University

Principal Investigator
Yoshiaki Sato



Target Disease (Applications)	Perinatal brain damage (Hypoxic Ischemic Encephalopathy: HIE)
Abstract	Multilineage-differentiating Stress Enduring (Muse) cells exist in bone marrow, skin, adipose, and other mesenchymal tissues, as well as in the connective tissues of many organs. So far, our non-clinical study with HIE model rats showed that Muse cells administered intravenously were detected in the injured brain, and ameliorated behavioral and learning impairments and movement abnormalities. The administration of Muse cells should be a promising therapy for HIE.
Advantages	Muse cells have the potential to self-renew and can differentiate into various types of somatic cells. Moreover, Muse cells readily integrate into injured sites and mediate tissue repair via tissue-specific differentiation.
Patent Information	Filed patent application
Market Overview	As the frequency of occurrence of HIE is 2 to 4 people per 1,000 live births, but the social impact is considered to be great.
Stage of Development	We evaluated the treatment effect and safety with clinical grade Muse cells-based product, CL2020 in non-clinical studies and performed several experiments to reveal the underlying mechanism of the treatment effect of the Muse cells on HIE. We have just proceeded to an investigator-initiated clinical trial.

Project Title

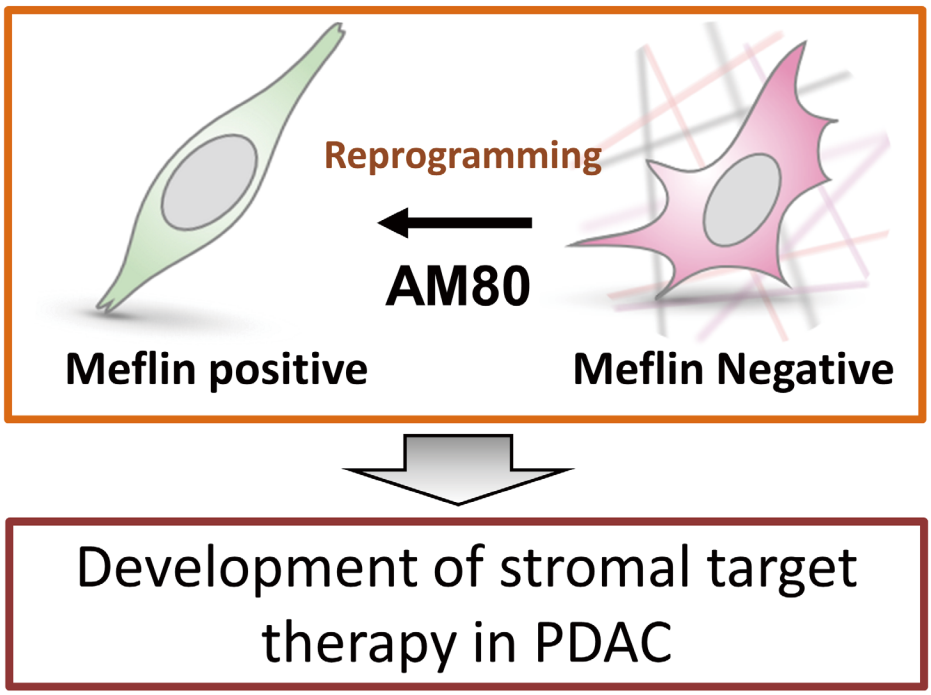
Open-label phase I/II investigator-initiated clinical trial based on a drug repositioning approach that reprograms the stroma of pancreatic cancer

Organization

University of Tokyo

Principal Investigator

Mitsuhiro Fujishiro



Target Disease (Applications)	Unresectable pancreatic cancer Combination therapy with standard therapy
Abstract	The object of this study is to perform an investigator-initiated clinical study to investigate the effect of AM80 on pancreatic cancer with a combination of conventional tumoricidal agents including gemcitabine and nab-paclitaxel.
Advantages	MIKE-1 is a drug that can be an enhancer of a new concept that greatly improves the drug distribution of anticancer drugs in the cancer stroma, and there is no similar drug approved by the regulatory affairs for this purpose at this time.
Patent Information	Patent Application 2020-110560
Market Overview	Untreated, unresectable pancreatic cancer patients(Stage III or IV)(Japan 14,000,US 29,000, Rationale: Pancreatic cancer clinical practice guidelines 2019,Cancer.Net https://www.cancer.net/)
Stage of Development	Phase I / II investigator-initiated clinical trial

Project Title

Multicenter clinical trial of the Patient-Specific Cardiac Support Device (CSD) with less constraint on RV for Dilated Cardiomyopathy

Organization

Nagoya University

Principal Investigator

Toshiaki Akita

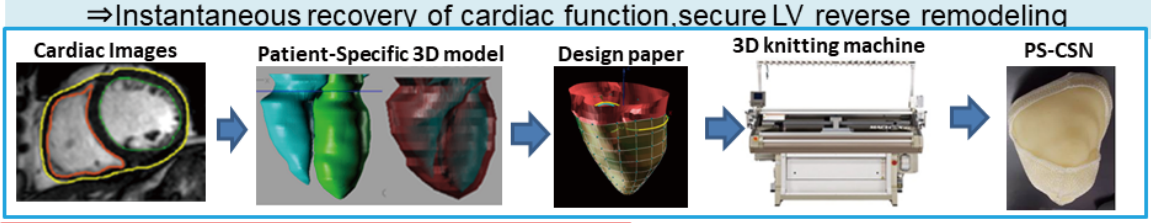
New Innovative Treatment for advanced Heart Failure:

Patient-Specific Cardiac Support Net (PS-CSN):

✓ Personalized designe from CT or MRI images（Patented in US, EU, CN, JP)

✓ Less constraint on RV side（Patented in US, CN, JP)

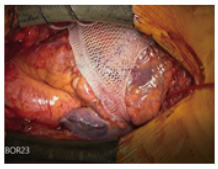
⇒Instantaneous recovery of cardiac function,secure LV reverse remodeling



Sakigake First tract Approval System (2020.Jun)

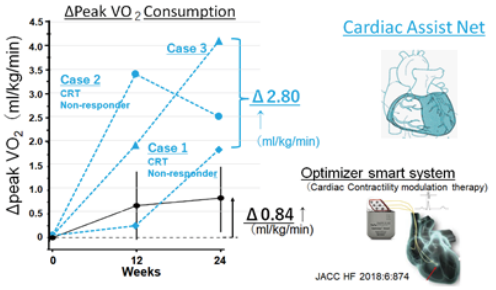
Multi-institutional Clinical trial underway（jRCT s042180025)

PS-CSN



		術前	術後12週	術後24週
Case 1	Peak VO2 (ml/kg/min)	12.5	12.7	14.3
	6MWT(m)	576	630	611
Case 2	Peak VO2 (ml/kg/min)	11.9	15.3	14.4
	6MWT(m)	411	522	555

Benefits: Improvement in Exercise Capacity by Cardiac Assist Net - Comparison with Newly Approved Device for HF Treatment



Target Disease (Applications)	Idiopathic dilated cardiomyopathy (DCM) Secondary cardiomyopathy Ischemic cardiomyopathy
Abstract	Multicenter clinical trial will be conducted to evaluate the safety and the usefulness of the Patient-Specific Cardiac Support Device (PS-CSD) with less constraint on RV for Dilated Cardiomyopathy.
Advantages	Patient-specific design → Less invasive and more effective Less constraint on RV → Preserve RV diastolic function and cardiac output Multi-scale & multi-physics cardiac simulation by UT-Heart Inc.→Select the suitable candidate and predict the postoperative cardiac function
Patent Information	Basic patent : registered, Method of creating design paper for patient-specific heart correction net: PCT→US, EP, CN, JP registered, Heart correction net : JP,US, EP, CN registered Registered design : JP(2), CN(1), US(2), EP(1)
Market Overview	Huge market for heart failure treatment (620 millions people in US) (Japan; 2,000 cases/year, 7 billion yen/year) Superior technology to competitor (Mardil: Acorn CorCap successor)
Stage of Development	To establish the safety of this device through small feasibility (First in Human study) in 2019 To establish the efficacy for improvement in cardiac function, cardiac remodeling indices, and QOL through investigator-initiated feasibility clinical trials in 2022, and pivotal study in 2023.

Project Title

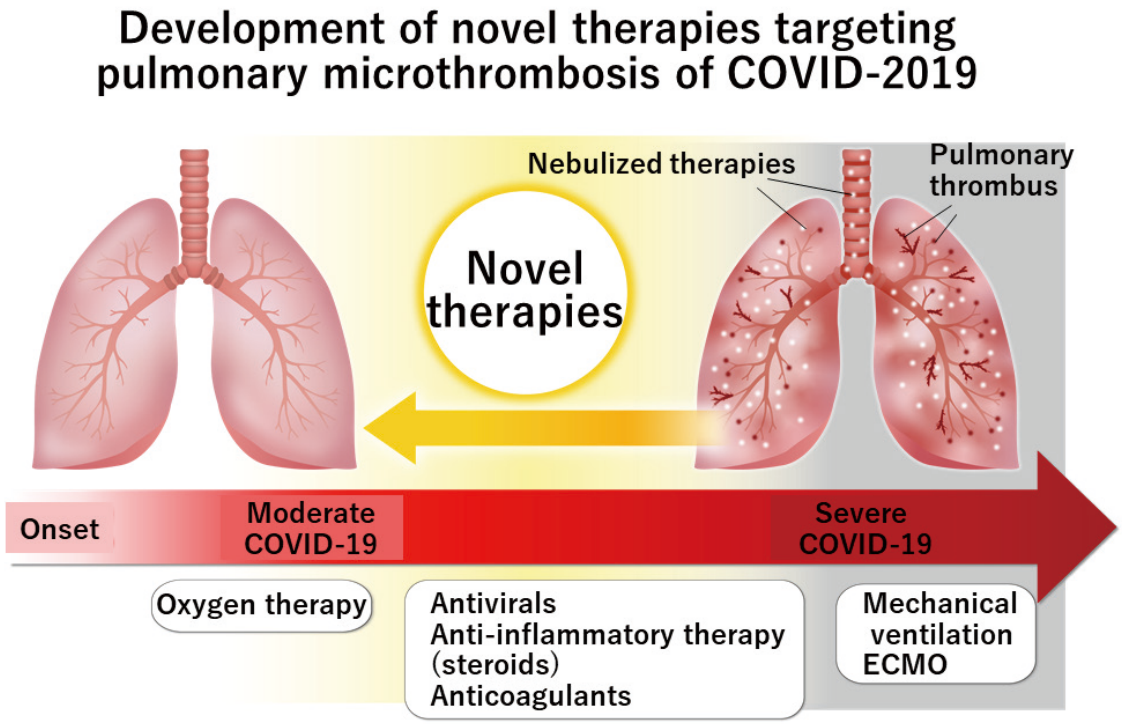
Development of novel therapies targeting pulmonary microthrombosis of coronavirus disease 2019

Organization

Nagoya University

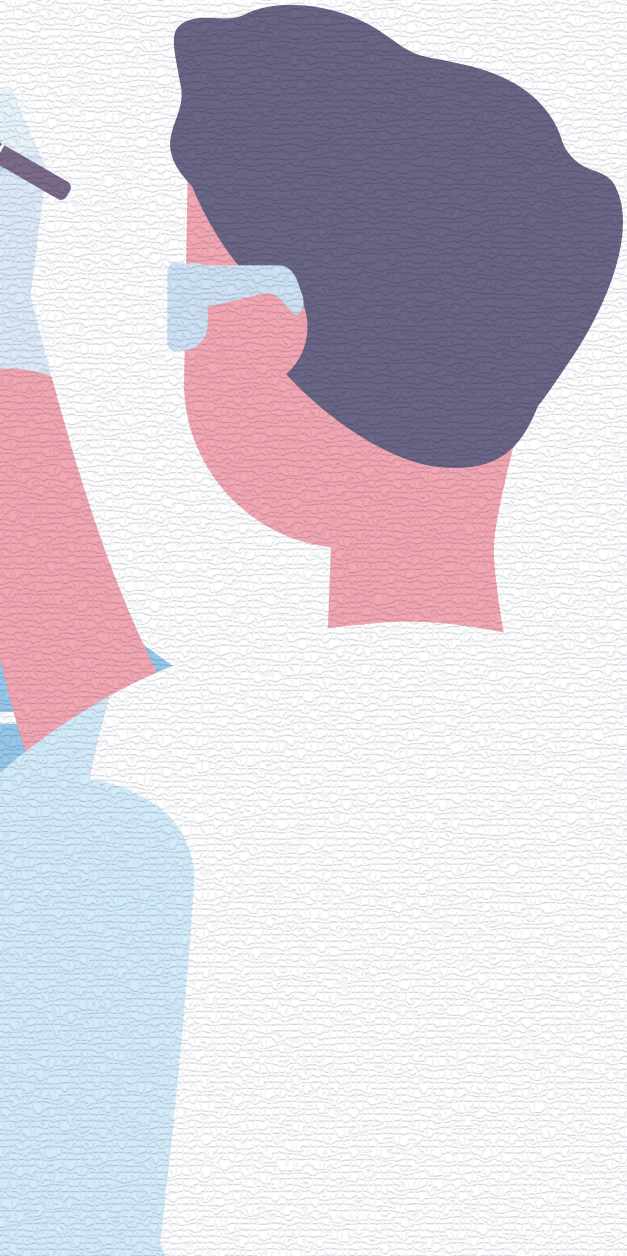
Principal Investigator

Yukari Goto



Target Disease (Applications)	Severe coronavirus disease 2019 (COVID-19)
Abstract	A feature of SARS-CoV-2 pathogenesis is COVID-19-associated coagulopathy, characterized by multiple pulmonary microthrombosis. Nebulized pharmacotherapies targeting multiple thrombosis are expected as novel therapies for severe COVID-19. We have established a research platform such as selection criteria for patients and an evaluation system for confirming safety. We are preparing for investigator-initiated clinical trial.
Advantages	Conventional therapies (antivirals, steroids, and anticoagulants) have not improved the prognosis of severe cases of COVID-19. Novel therapies (nebulized therapies) targeting multiple pulmonary microthrombosis are suitable for the pathology of severe cases and can be expected to improve the prognosis.
Patent Information	None
Market Overview	Cumulative number of patients with COVID-19: About 1.7 million. The market will be large when a new epidemic occurs in the future.
Stage of Development	We are preparing for investigator-initiated clinical trial.

3 Services & Facility



Clinical Trials

Center for Advanced Medicine and Clinical Research

- **Project Management**
- **Creating Documents**
  - — Protocol
  - — Investigator's Brochure
  - — Informed Consent Form
  - — Manufacturing Related Documents of GMP for Investigational Drugs
- **Creating Standard Operating Procedures**
  - — Operating Procedure for Outsourcing to Study Coordinating Committee
  - — Operating Procedure for Clinical Study Coordinating Committee
  - — Operating Procedure for Issuing Protocol and a Sample of Case Report Forms
  - — Operating Procedure for Investigator's brochure
  - — Operating Procedure for Creating an Informed Consent Form
  - — Operating Procedure for Handling Safety Information
  - — Operating Procedure for Keeping Records
  - — Operating Procedure for Efficacy and Safety Evaluating Committee
  - — Operating Procedure for Auditing
  - — Operating Procedure for Issuing the Clinical Study Report
  - — Operating Procedure for Sample Storage/Management/Transport
  - — Operating Procedure for Study Drug Management

● Preparation phase

Data Coordinationg Center

- **Statistical Analysis**
  - — Plan for Statistical Matters of Clinical Study (Trial Design, Sample Size, Proposal and Description of Statistical Analysis Part)
  - — Creating the Statistical Analysis Plan (SAP)
- **Data Management**
- **Creating Standard Operating Procedures**
  - — Operating Procedure for Monitoring
  - — Operating Procedure for Data Management
  - — Operating Procedure for Case Registration and Assignment
  - — Operating Procedure about Biostatistics

Patent

- **Support for Patent Application**
- **Support for Patent Investigation**

- **Support for Clinical Research**
  - — Support for Minister in Verifying Conformance to Guidelines(Regenerative Medicine, Gene Treatment, Advanced Therapy)
  - — Consultation with PMDA
  - — Clinical Research Coordination
  - — Monitoring(Investigator Initiated Study)
  - — Study Drug Management at Study Coordinating Office
  - — Study Drug Management
  - — Support for Administration Office
  - — Auditing

● Implementation phase

- **Support for Clinical Research**
  - — Support for Data Monitoring Committee
- **Statistic Analysis**
  - — Programming and Data Analysis in accordance with SAP, Mock
  - — Gene Expression / DNA methylation Data
  - — SNP/CNV Data
- **Data Management**
  - — Maintenance of Case Registration and Assignment System
  - — Enrollment and Assignment
  - — Maintenance of Data Management System
  - — Data Management

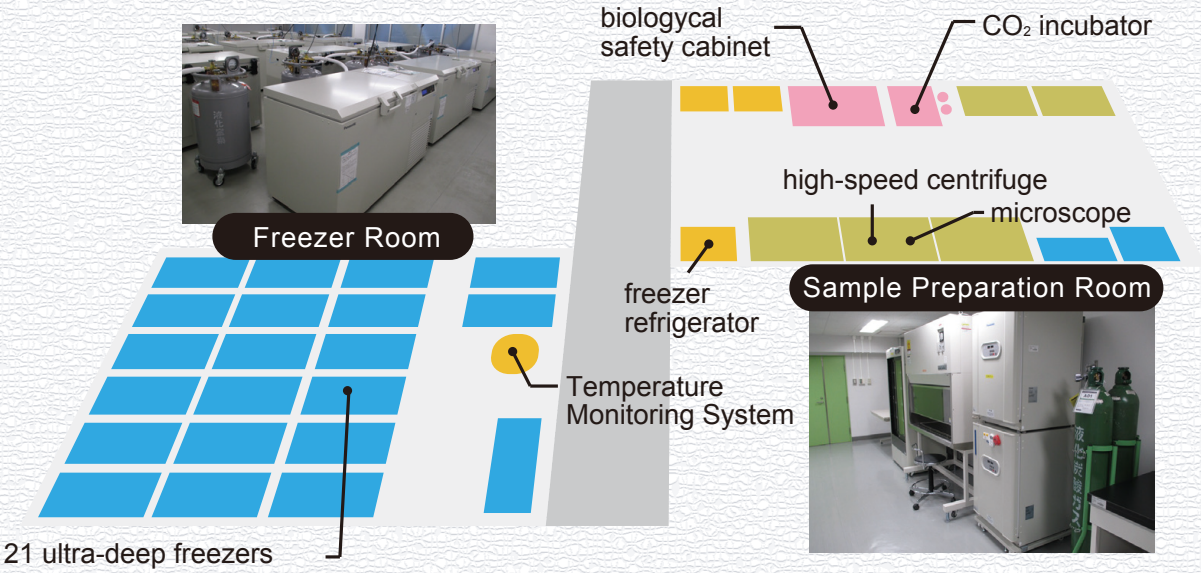
● Reporting phase

- **Issuing the Report**
  - — Clinical Study Report
  - — Statistical Analysis Report

Regulatory Affairs

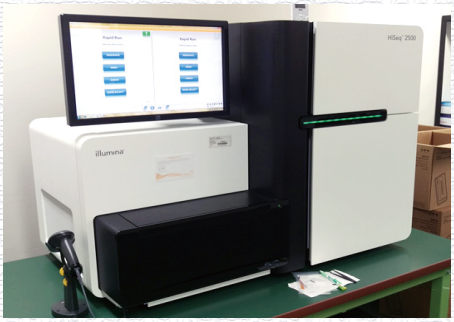
- **Communication with Regulatory Agencies**

Bio-bank Sample Storage Room

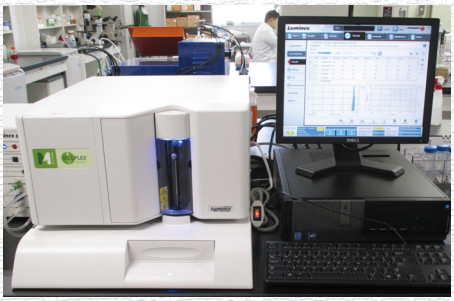


Major Equipment

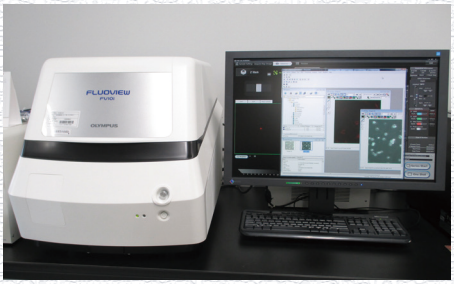
FACSAria™ Fusion (BD)



HiSeq 2500 (Illumina)



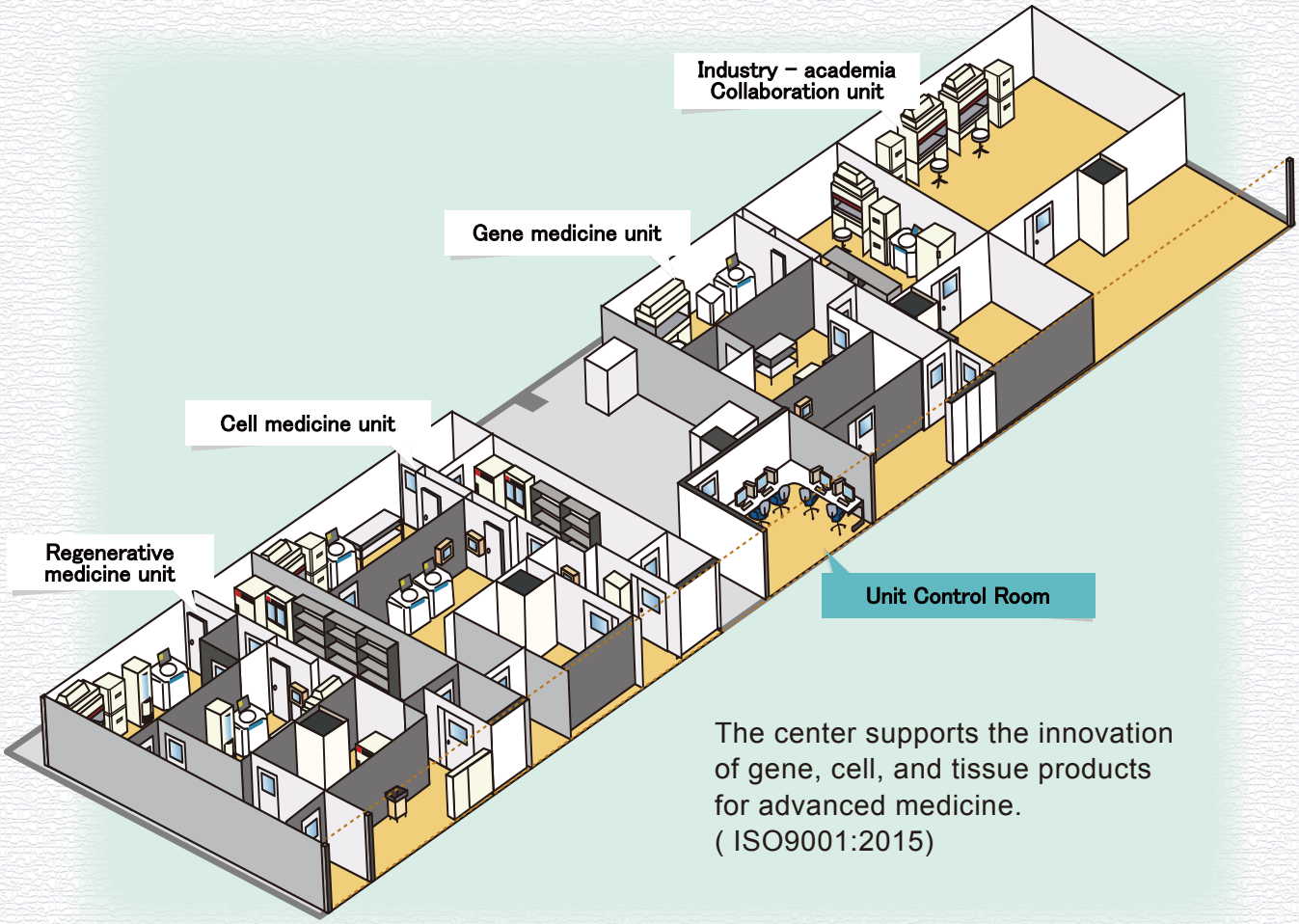
Luminex 200 (MERCK MILLIPORE)



FLUOVIEW FV10i (OLYMPUS)

Center for Advanced Medicine and Clinical Research

Bio-material Preparation Unit



The center supports the innovation of gene, cell, and tissue products for advanced medicine.
(ISO9001:2015)

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