Our Research Interests

1. Oncology

1-1. Small molecule programs

1-2. Biologics programs

2. Pain / Neuroscience

2-1. Targets or mechanisms for treatment of “chronic pain (nociplastic pain) based on CNS abnormality”

2-2. Vision loss caused by retinal degeneration

2-3. Targets or mechanisms to promote rehabilitation effects after stroke

3. Cardiovascular and renal diseases

3-1. Novel targets and lead compounds

3-2. Drug Delivery System

3-3. iPS

4. Rare diseases

4-1. Monogenic / Rare diseases

4-2. Gene therapy

4-3. Small molecule

5. Other diseases

5-1. Microbiome-related diseases

5-2. Vaccine

6. Cell therapy

6-1. Cell potentiation

6-2. Adoptive T cell therapy for cancer

7. Technology and related research

7-1. Novel nucleic acid therapeutics

7-2. Novel peptide therapeutics

7-3. Technology for membrane protein preparation

1. Oncology

1-1. Small molecule programs

I. Immuno-Oncology/Cancer Microenvironment

- Novel druggable-targets/compounds for cancer immunotherapy with tumor specificity and patient stratification strategy
- Unique drug discovery programs aiming the booster of tumor antigenicity

II. Growth/Survival signals

- Programs focusing on specific inhibitors for tumor driver or drug-resistance mutation (including fusion and variant)

III. Epigenetics

- Epigenetic targets with biological validation
- Small molecule compounds targeting methyltransferase, demethylase and chromodomain
- An approach to elucidate the mechanism of action of small molecule compounds targeting methyltransferase, demethylase and chromodomain for patient stratification and/or efficacy prediction

IV. Model and technology

- Unique *in vitro* or *in vivo* models of leukemia or reflecting cancer immunity in human
- Methods for predicting antigenicity of neo-antigen with more efficiency and accuracy than current available algorisms
- A unique drug discovery approach to target drug tolerant “persister” cells derived from clinical sample
- Unique drug discovery platforms targeting signal molecules such as small GTPase, phosphatase, and scaffold protein, which are currently thought to be low druggability
- Technology platform to analyze drug combination effect

<Not Interested in>

- Programs without key points of differentiation from competitors
- “Best-in-class” programs without strong differentiating points from current available therapy
- Targets without *in vitro* assay system

- Just controlling metastasis process (e.g. cell motility, cell adhesion, etc.)
- Regulation of biological processes essential for homeostasis

1-2. Biologics programs

"Biologics" mean antigen-binding proteins such as antibodies, antibody-like formats etc.

I. Novel molecular targets/mechanisms or technologies for the development of "Biologics" for cancer therapy related to

- Non-apoptotic/highly-immunogenic cell death or interrupting tumor (or virus)-evoked immune evasion pathways
- Cancer immune suppression, immune escape or immune checkpoints
- Refractory/resistant cells to the existing-therapy
- Cancer-associated fibroblasts or mesenchymal stem cells

II. Novel adjuvants that can activate intracellular immune molecule(s)

2. Pain / Neuroscience

2-1. Targets or mechanisms for treatment of "chronic pain (nociplastic pain) based on CNS abnormality"

- Normalization of rewarding-aversion system
- Immobilization and overwriting of pain memory
- Prevention of transition from acute to chronic pain
  - Desirable if there are ideas for animal-to-human translation

<Not Interested in>

- Diseases : acute pain, migraine, simple nociceptive pain
- Targets : Opioid receptor system, common antidepressants

2-2. Vision loss caused by retinal degeneration

- Breakthrough mechanisms/agents to maintain visual function and suppress retinal pigment epithelium cell death for geographic atrophy
- Novel vascular protective targets/agents for diabetic retinopathy/diabetic macular edema
- Novel neuroprotective targets/agents to enhance survival of retinal ganglion cells for glaucoma
- Novel drug delivery systems enabling sustained release in retina

<Not interested in>

- Well-known antioxidants, glutamate receptor antagonists, intraocular pressure lowering agents, known targets for angiogenesis, and anti-inflammatory targets or agents

2-3. Targets or mechanisms to promote rehabilitation effects after stroke

- Novel targets and mechanisms leading to reconstruction of neural network. Druggable targets such as receptors, transporters, enzymes are preferable
- Novel approaches to enhance neuronal network reconstitution or synapse formation including medical devices used in combination with drugs
- Novel imaging technology or PET probe to evaluate reconstitution of neuronal network and synapse formation

<Not Interested in>

- Targets for neuroprotection, anti-hypertension, anticoagulants or brain edema reduction
- Cell therapy

3. Cardiovascular and renal diseases

3-1. Novel targets and lead compounds

- Small molecules:SERCA2A activator, phospholamban binder
- Intractable immune-mediated renal diseases
- Novel treatment of Peripheral Arterial Diseases (PAD) and Cerebral Vascular Diseases (CVD)

3-2. Drug Delivery System

(same as 7-7)

- Targeted delivery to heart (for small molecules, oligonucleotides, peptides, etc.)
- Oral delivery of macrocyclic peptide

3-3. iPS

- Methodology of atrial-like or ventricular-like cardiomyocyte differentiation from iPS
- Functional screening system of intractable kidney diseases using differentiated iPS

4. Rare diseases

4-1. Monogenic / Rare diseases

- Innovative therapeutics for genetically defined diseases with high unmet medical needs (severe/progressive/high lethality)

4-2. Gene therapy

- Technological innovations relevant to gene therapy, such as novel vectors or delivery systems which can overcome existing problems (ex. gene size, immunogenicity, risk related to gene insertion, administration route) of current

technology.

4-3. Small molecule

- Novel chemical chaperons or function-activator of loss-of-function mutant proteins in monogenic rare diseases.

<Not Interested in>

- Indication: Rare cancer
- Gene therapy: Gene insertion into host genome

5. Other diseases

5-1. Microbiome-related diseases

I. Novel molecular targets/mechanism

- Innovative therapeutic targets/mechanisms of microbiome-related diseases focused on gut, oral, and skin microbiome
- Small molecule compounds that can potentially modulate microbiome-disease outcome

<Not Interested in>

- Fecal microbiota transplantation
- Live engineered bacteria

5-2. Vaccine

I. Novel antigen candidates/strategy for immunotherapy on

- Cancer
- Allergic rhinitis
- Food allergy
- Life style-related diseases
- Rare diseases
- Infectious diseases

【Interested in】

- Novel antigen/peptide/nucleic acid/other materials which modulate immune system (antibodies, helper T cell, cytotoxic T cell, regulatory T cell, regulatory B cell, etc.)
- Novel strategy for immunotherapy/vaccine

6. Cell therapy

6-1. Cell potentiation

I. Genetically modifying methods

- Functional potentiation of allogeneic mesenchymal stem cell (MSC) by gene transduction

II. Non-genetically modifying methods

- Isolation/preparation of novel type of somatic stem/progenitor cells or iPS-derived cells that have patentability to potentiate cell functions compared to general MSC

III. Biomaterial and medical devices

- Creation of novel biomaterial to potentiate cell functions
- Novel application of medical devices to sustain the cell viability and functions

6-2. Adoptive T cell therapy for cancer

I. Novel technologies for high quality allogeneic T cells including iPS/ES cell-derived ones

II. Novel technologies to potentiate T cells

III. Novel non-viral gene transfer system for rapid production of CAR-T

IV. Novel high-throughput platform for generation and characterization of CAR-T.

V. Novel platform to analyze relationship between CAR construct and antitumor activity

7. Technology and related research

7-1. Novel nucleic acid therapeutics

I. Novel mRNA modification methods suitable for nucleic acid therapeutics

II. Novel molecular targets suitable for nucleic acid therapeutics

III. Novel delivery platforms for systemic or local administration of antisense oligonucleotides, siRNA or modified mRNA

- DS owns chemically modified ENA® oligonucleotides technology. We welcome the proposal which reveal a synergistic effect with our technology.

<Not Interested in>

- Viral vectors, delivery systems specific for plasmid DNA therapy

7-2. Novel peptide therapeutics

I. Novel library technologies applicable to peptides, non-canonical peptides, and peptide mimetics to discover potent ligands against undruggable targets

II. Novel cell-permeability assay systems for peptides without fluorescent functional groups

III. Novel technologies to extend half-life (e.g. once a month dosing in human) of existing peptides/proteins by fusing novel peptide

- Species cross reactivities are required (mice, rat, monkey and human)
- This wish includes peptide tags that bind to some proteins/cells and append recycling functions
- Preferably less than 5 kDa peptide
- Immunogenicity should be considered

<Not Interested in>

- PEGylation, large protein fusion, albumin binding domains derived from protein A/G or related motifs

7-3. Technology for membrane protein preparation

I. Large-scale production method of multi-spanning transmembrane proteins retaining their native structures and functions

- "Large-scale" means more than milligram scale.
- Multi-spanning transmembrane proteins prepared by the method can be used in various experiments such as bio-panning and screening.
- Capabilities for functional/structural validation as well as sample preparation are required.
- Capabilities for structural analyses of multi-spanning transmembrane protein using X-ray crystallography or cryo-EM are preferable.

<Not Interested in>

- Production method for single-pass transmembrane proteins (such as RTKs)

7-4. Novel bispecific antibody therapeutics

I. Novel targets suitable for CD3 bispecific antibodies

- DS owns our original monoclonal antibodies for human and cynomologus CD3.

II. Novel coupled targets for bispecific antibodies

For both of I. and II.

- *In vitro* assay systems and animal disease models to evaluate antibodies are required.
- Having specific monoclonal antibodies for the targets is preferable.

7-5. Novel technologies for gene therapy

I. Novel technologies engineering rAAV vectors for lifelong gene therapy

- Technologies enabling administration of the rAAV vector at least two times to the same patient
- Technologies enabling long/stable expression of gene of interest by rAAV vector in proliferating cells

7-6. *In silico* modeling

I. Precise *in silico* ADME prediction method based on chemical structures

- Artificial intelligence methods for predicting solubility, metabolic stability, plasma protein binding, or membrane permeability using novel molecular descriptors
  - Methods which will be established by utilizing training dataset of tens of thousands of compounds

<Not Interested in>

- Methods using existing types of molecular descriptors including atom types, 2D substructures, and topological (connectivity or path) fingerprints

7-7. Drug Delivery System

(same as 3-2)

- Targeted delivery to heart (for small molecules, oligonucleotides, peptides, etc.)
- Oral delivery of macrocyclic peptide