# Daiichi Sankyo Business Development

# Areas of Interest

## Oncology

### 1-1. Biologics Programs

I. **Novel molecular targets /mechanisms for the development of "Biologics" for cancer therapy. "Biologics" includes monoclonal antibodies, antibody fragments, bispecific antibodies, and CAR-T.**

- Monoclonal antibodies or antibody fragments which are specific to tumor antigens
- Target(s) involved in tumor progression via modulation of cancer neuronal crosstalk across all cancer types (priority should be given to certain themes with an evaluation model)
- **Not of interest:** Antibody-Drug Conjugate (ADC) programs

II. **Multi-targeting technology/approach to overcome resistance with tumor heterogeneity in T-cell engaged therapies (CAR-T/bispecific Abs)**

III. **A mechanism that uses an external force (e.g. near infrared light, X-ray, ultrasound and so on) to change the activation state of compounds/biologics, elicits an anti-tumor effect**

IV. **Conditionally active biologics technologies that enhance cancer specificity by using environmental factors unique to tumor tissues. Clinical information which support the concept of conditionally active technologies.**

- **Not of interest:** Protease-activated masked antibody and pH dependent antibody

V. **Novel technology or proposal of combination partner drugs to enhance tumor microenvironment penetration/delivery of biologics (including brain tumor)**

VI. **Novel drug and/or gene delivery with bacteria, which is effective even in heterogeneous tumors**

### 1-2. Small Molecule Programs

I. **Phenotypic screening system/technology:**

- Novel phenotypic screening system reflecting tumor heterogeneity, microenvironment or drug-resistance to achieve complete response
- Novel technology for drug-target identification using phenotypic screening system

II. **RNA drug discovery research platform: assay platform/systems to evaluate splicing**

**modulators, any RNA targets including non-coding RNA or mRNA which work as tumor driver**

III. **Assay platforms to target changes in spatial genome organization (3D genome) or in cell lineage/plasticity of cancer cells**

IV. **Novel technologies for identification of "monovalent" (non-chimera) protein degrader and stabilizer ("molecular glue") as an alternative approach for protein degradation/stabilization**

### 1-3. Assay Platform and Targets for Immuno-Oncology (Small Molecules/Biologics)

I. **Novel assay platform (in vitro/ex vivo/in vivo assays/screening systems) for immuno-oncology research targeting factors in tumors, T-cells, or tumor microenvironment**

- Platform enabling the prediction of clinical efficacy of compound in human as a single-agent or combination therapy
- Platform enabling the identification of novel target molecules critical for (i) resistance to immune checkpoint inhibitor (ICI) or (ii) synergistic combination effects with ICI

II. **Innate lymphoid cell (ILC) target(s) or target screening aimed at enhancing antitumor effect**

- Themes with a confirmed mechanism in human-derived samples will be prioritized

## Specialty Medicine

### 2-1. Monogenic / Rare diseases

I. ***Innovative therapeutics for genetically defined rare diseases with high unmet*** **medical needs (e.g. significant morbidity and/or mortality) that are combined with new approaches such as**

- Novel technology for tissue/cell specific modulation of disease target (e.g. tissue-specific delivery/modulation of AAV therapy).
- Novel target of gene therapy including splicing modulation (e.g. trans splicing, mRNA repair).
- Novel technology to prevent generation or activity of neutralizing antibodies in the blood in AAV therapy
- **Not of interest:** Rare cancer
- **Not of interest:** Genome editing

## 2-2. Immune-related diseases

I. **Novel therapeutic targets/mechanisms involved in over-activation of immune system (e.g. cytokine storm syndrome) which is associated with infection, ageing and mitophagy.**

II. **Novel therapeutic targets/mechanisms for depleting specific pathogenic immune cells (e.g. autoantibody-producing plasma cells and self-antigen specific T/B cell)**

III. **Novel therapeutic targets/mechanisms in refractory immune-mediated end-organ diseases (e.g. neuro-inflammation diseases, nephritis, and vasculitis)**

## 2-3. Ophthalmology

I. **Novel technologies and/or biological mechanisms/targets for gene therapy in eye diseases (e.g. vectors for intravitreal injection, minigenes amenable for AAV vectors, novel target molecules applicable to gene therapy).**

II. **Novel pathological biomarkers based on diagnostic imaging and AI technology in ophthalmology.**

## 2-4. Pain

I. **Novel molecular targets or therapeutics to prevent "chronic pain state" development.**

- Chronic pain state: Altered gene expression which maintain peripheral and central sensitization to amplify nociceptive stimuli.
- Therapeutics: oligonucleotide, gene therapy, and new modalities

II. **Novel technologies of DDS to peripheral sensory neuron or spinal neuron (oligonucleotide, gene therapy, and new modalities).**

## 2-5. CNS diseases

I. **Psychiatric diseases**

- Technology, device, and index for precision medicine for psychiatric disease (patient stratification)
  - Stratification by brain circuit: Research on brain dysfunction caused by abnormalities in specific brain regions and brain circuits
  - Stratification by brain function: Technology, indexes, and analysis methods that accurately and objectively measure human brain function and mental state
  - Vitalization of facial expressions, speech, sleep, etc.: Technologies such as wearable devices that easily and simply substitutes human brain functions

- Animal behavior analysis technology (digital phenotyping technology) using continuous and comprehensive observation

- Value improvement of existing drugs for Psychiatric diseases
  - Priority diseases includes schizophrenia, autism spectrum disorders and genetic diseases.

- Novel idea/approaches to improve efficacy of existing therapeutic compounds or endogenous bio-active biomolecules such as neuropeptides.

**II. Neurodegenerative diseases**

- Elucidation of mechanisms underlying misfolding of neurodegenerative disease-related proteins such as Amyloid β, Tau, α-syn, PrP, TDP-43, and Htt (polyQ proteins), and their therapeutic approaches.
  - Novel approaches for inhibition, degradation or elimination of misfolded proteins.
  - Novel approaches to identify specific binders to intrinsically disordered regions of misfolded proteins.
  - Novel therapeutic targets and/or modulators for formation of liquid–liquid phase separation.
  - Elucidation of mechanisms underlying the generation of different conformational strains from the same protein, and approaches for the identification and isolation of each strain.
- Novel technologies for research and diagnosis of neurodegenerative diseases.
  - Disease-relevant assay systems and animal models. (For example, the model reflecting the abnormal structure of misfolded protein from patients, possible disease mechanism, etc.)
  - Novel methodologies for diagnosis and stratification of patients based on misfolded protein.
  - Novel technologies or digital devices to address cognitive impairment in dementia.
- Novel approaches to identify druggable targets other than neurodegenerative disease-related protein itself.

## 2-6. Organ damage

**I. Therapeutic approaches for non-syndromic deafness**

- Novel therapeutic targets, mechanisms and in vitro/ in vivo assay system for non-syndromic deafness (especially cochlear neuropathy) resulting from monogenic defects.

**II. Therapeutic approaches for monogenic cardiac disorder**

- Novel therapeutic targets, mechanisms and in vitro/ in vivo assay system for monogenic cardiac disorder (e.g. dilated/hypertrophic cardiomyopathy).

## Cell Therapy

**I. Novel technologies for adoptive T cell therapy**

- Novel molecular targets/mechanisms to potentiate T-cell functions
- Novel molecular targets/mechanisms to enhance T-cell infiltration into tumors in vivo
- Novel technologies for "off-the-shelf" T cell generation
- Novel technologies for screening and maturation of target binding molecules suitable for loading on CAR-T/TCR-T

**II. Novel technologies for allogenic cell transplantation**

- Novel types of universal donor stem cells allowing the stem cell derived products to treat most patients
- Novel technologies for cell modification and/or biomaterials/devices to maintain/enhance cell viability and functions in vivo
- Novel technologies for biomaterials/devices to protect engrafted cells from immune recognition while simultaneously supplying nutrients

## Vaccine

**I. Expansion of LNP-mRNA technology platform**

- Technologies for prediction/identification of antigen candidates for emerging infectious disease vaccines
- **Most interested in:** Exploring immunological correlates of protection against COVID-19 and development of analytical methods for efficacy biomarkers required for clinical PoC and biomarkers for enhanced diseases

## Technology and Related Research

### 5-1. Novel nucleic acid therapeutics

**I. Novel molecular targets in genetic disorders suitable for nucleic acid therapeutics**

**II. Novel delivery platforms or organ selective targeting ligand for antisense oligonucleotides, siRNA or mRNA**

**III. Novel gene editing technologies unaccompanied by DNA double strand break**

- DS owns technology for chemically modified ENA® oligonucleotides and welcomes proposal which may work synergistically with this technology.

## 5-2. Targets for protein therapeutics

### I. Novel targets for bispecific antibody therapeutics

- Novel targets and their combinations to show or to be expected to have synergistic biological activities or novel biological activities which can be brought by bispecific antibodies, such as activating/inactivating signaling pathways,
  - Specific monoclonal antibodies to each target should be available. Fragment antibodies, other scaffold proteins and engineered natural ligand are acceptable as formats of binders.
  - Animal disease models and/or translational research (tissues or cells from patients) are preferable.
  - Our focus areas are oncology as well as non-oncology such as rare diseases and immune disorders.

## 5-3. Novel antibody/protein therapeutics

### I. Novel antibodies/proteins that can be conditionally activated/switched dependent on disease condition or environment

- Antibodies/proteins which can be activated only with specific disease condition.
  - Specific diseases include tumor, rare diseases and immune disorders.
  - The biological conditions include concentration of certain molecules, pH (for non-oncology only), and temperature etc.
  - Proteins include cytokine or protease
- **Not of interest:** pH dependent antibodies for cancer therapeutics
- **Not of interest:** Masked-antibodies for cancer therapeutics
- **Not of interest:** Masked proinflammatory cytokines (e.g.IL2, INFalpha, IL-12, 4-1BB agonist) that act only on tumor microenvironment.

## 5-4. Novel peptide therapeutics

### I. Novel chemical modification to stabilize peptides with α-helical or β-sheet-like structures and to enhance cell-permeability for regulation of intracellular protein-protein interaction

## 5-5. Modality technologies for targeting intracellular molecules

I. **Technologies related to the discovery/design of antibodies which can move into cytosol (or nucleus) of target cells (i.e. cell-permeable antibody). These antibodies are required to translocate into cells in less than 100 nM range.**

II. **Technologies for identifying hit/lead peptides that possess both cell-permeability and target binding activity. These peptides are required to be effective in cell-based assays in equal to/less than low-micromolar range.**

III. **Methods to quantitatively analyze the entry of the above antibodies/peptides into cells.**

- Not of Interest: Fusions with known cell-penetrating moiety such as CPP (e.g. R8, TAT) and toxic protein.

## 5-6. 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 strict regulation of on/off or the degree of the expression of the gene of interest. (Technologies utilizing existing technologies such as tet-on/off are out-of-scope.)

## 5-7. Novel functions involved in the maintenance and control of cellular protein homeostasis

- Novel molecules/functions involved in the maintenance and control of cellular protein homeostasis
- Elucidation of their physiological roles.

## 5-8. Hit finding & hit to lead technology for small molecules

I. **Novel hit/lead finding technology targeting “undruggable” proteins or RNAs**

II. **Novel drug discovery technology for the targets without X-ray structures or known small molecule ligands**

- Novel method of virtual screening, ligand estimation and drug design
- Protein structure prediction or binding site estimation
- SBDD based on the modeling using NMR spectroscopic data

III. **Technologies of creating unique chemical library**

- Methods of creating chemical library using non-traditional chemical reactions, such as electrochemical reactions, photochemical reactions, enzymatic reactions etc.
- Synthetic biological methods of creating natural product-related library

## 5-9. In silico technologies to support small molecule drug discovery

**I. Development of quantitative analytical method of protein surface and its application to target classification for appropriate modality selection**

**II. Novel in silico platforms for small molecule drug discovery**

- In silico design method of PROTACs
- Target identification methods appropriate for small molecule drug discovery program using public database such as 'omics' (genomics, transcriptomics, proteomics, metabolomics) data

**III. Novel computational chemistry approaches**

- Novel chemical descriptors based on quantum chemical parameters
- Fast quantum chemical calculation method

## 5-10. Emulation of human ADME and bioanalysis

**I. High-throughput in vitro assay systems to predict human BBB (blood-brain barrier) and/or BRB (blood-retinal barrier) permeability with high accuracy**

**II. *In vitro* cellular assay systems which accurately recapitulate drug metabolism and transport in humans**

- Novel cellular assay systems to evaluate following:
  - Metabolism by non-CYP enzymes, such as UGT, SULT, AO, FMO, etc., in liver
  - Secretion and re-absorption (and metabolism) in kidney
  - Simultaneous measurement of metabolism and transport in gut
- Organ-on-a-chip technologies
- **Not of Interest:** Non-human cellular assay systems

**III. Novel bioanalysis technologies for new modality ADME research**

- Novel bioanalysis technologies to characterize and quantitate biotransformation of biologics (antibodies, ADC, etc.)
- Novel and sensitive label-free imaging technology applicable to biodistribution research for various drug modalities (small and middle molecule compounds, biologics, cells,

virus, etc.)

- **Not of Interest:** Well-known methods (conventional LBA, LC/MS, Alu-PCR, MRI, ARG, PET, IVIS, imaging MS etc.), although it is acceptable if remarkable progress is expected

## 5-11. DDS

### I. Novel cancer-specific delivery platforms for chemical compounds, antisense oligonucleotides and biologics

- Small molecule prodrug technology utilizing cancer-specific enzymes
- **Not of Interest:** Molecular modification and conjugation with antibody or synthetic polymer

### II. Novel DDS technologies for tissue specific-targeting

- Target tissues: brain, heart, skeletal muscle
- Novel carriers or other DDS technologies to deliver drugs to the tissues using physiological mechanisms such as receptor mediated endo/transcytosis
- **Not of Interest**: Technologies to physically open the BBB
- **Not of Interest:** Liver-selective nucleic acid delivery technologies

### III. Novel DDS technologies for enhancing drug permeability

- Examples of the technologies: enhancement of oral absorption of peptides and macromolecules, improvement of percutaneous absorption of low and middle molecule compounds
- **Not of Interest:** Technologies which physically open the tight junction.

## 5-12. In silico modeling

### I. *In silico* prediction methods for ADME parameters for peptides and nucleic acids

- Methods for predicting solubility, metabolic stability in plasma/blood and/or tissues, plasma protein binding, or membrane permeability using machine learning (including deep learning)