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)