June 2021

Wish List of Mitsubishi Tanabe Pharma

In order to find out opportunities for collaboration with you, we have made a list of research and technologies that Mitsubishi Tanabe Pharma is seeking. We look forward to working with you.

Target Indications

- Neurological diseases
  - Research seeds related to the following neurodegenerative diseases
    - Amyotrophic lateral sclerosis (ALS) and mitochondrial diseases (especially MELAS)
      - Therapeutic approaches related to the causal gene pathways are desirable
    - Multiple system atrophy and progressive supranuclear palsy
      - Mainly focus on responsible target discovery
    - Huntington's disease and spinocerebellar degeneration
      - Therapeutic approaches with small molecules to causal genes/proteins
    - Alzheimer's disease /frontotemporal dementia
      - Potential drug targets for stratified patients based on genetic information
    - Sleep disorders or dysphagia as comorbidities in neurological diseases
  - Research seeds related to the following neurodevelopmental disorders
    - Autism spectrum disorders (especially those associated with monogenic disorders and copy number variations)
    - Developmental epileptic encephalopathy with a genetic diagnosis
    - Sleep disorders in neurodevelopmental disorders

- Immuno-inflammatory diseases
  - Research seeds that are indicated for the following diseases and can be differentiated from existing drugs
    - Systemic lupus erythematosus (SLE)
    - Systemic sclerosis
    - Polymyositis/dermatomyositis (including Anti-synthetase syndrome)
    - Vasculitis (including Takayasu's arteritis)
  - Research seeds for rare antigen-specific autoimmune diseases

- Sensory organ diseases
  - Therapeutic approach directly to the causative gene or related to the pathway of the causative gene.
    - Hearing loss, Retinitis pigmentosa, Corneal dystrophy
  - Therapeutic approaches with technical information such as patient

stratification methods and markers

- Glaucoma, Age-related macular degeneration

Drug Discovery Technology

- Assay systems required for screening and proof of concept studies
  - ✧ Banks of clinical samples, cell models, and animal models for the diseases on this wish list
  - ✧ Technology for rapid differentiation of neural and glial cells from iPS cells or somatic cells of healthy subjects and patients with neurological diseases on this wish list
  - ✧ Contract research of gene expression of the above differentiated cells
  - ✧ Screening system using disease-specific iPS cells derived from patients with immuno-inflammatory diseases（plasma cell, Treg, $CD8^+$ Tcell）
  - ✧ Highly predictive organoids or organ/human-on-a-chip in humans (for neurological diseases on this wish list, kidney, muscle, cornea, retina, etc.), and (device) technologies that enable evaluation of cell functions in combination with these systems (contract research is also available)
  - ✧ Evaluation technology that mimics the blood-brain barrier to evaluate the loosening of the barrier function itself, rather than predicting permeability
  - ✧ Microphysiological System for high throughput
  - ✧ Technology that enables high throughput single-cell RNA-seq analysis such as using 384-well plates
  - ✧ In vivo models that can evaluate the excitatory and/or inhibitory functions of neurons in the brain at the single cell level (especially neurodevelopmental diseases on this wish list)
  - ✧ Immune cell function evaluation systems that can predict clinical effects (patient-derived cells are preferred)
  - ✧ In vitro evaluation systems of macrophage/dendritic cell, Tph/Tfh or $CD8^+$ T cell reflecting the pathogenesis of autoimmune diseases
  - ✧ In vivo human cell evaluation technology (humanized mice, especially for antigen-specific immune response and for autoimmune disease)
  - ✧ A clinically extrapolatable mouse model of autoimmune pulmonary hypertension
- Technologies related to oligonucleotide therapeutics (including oligonucleotide modification, formulation and non-invasive dosing devices)
  - ✧ Technologies that enable persistence in the central nervous system (CNS), controlled distribution in the brain, and delivery from the periphery to the CNS
  - ✧ Technologies that enable selective delivery and sustained localization

(muscle, cornea, retina, inner ear, etc.)

- ✧ Technologies that enable subcellular localization (especially in mitochondria)
- ✧ In vitro/in vivo evaluation methods with high accuracy for human prediction in each organ toxicity including liver, kidney, and CNS
- ✧ Mechanistic analysis of hepatic, renal, and CNS toxicity and mechanism-based avoidance methods
- ✧ Drug delivery system (DDS) for toxicity avoidance
- ✧ In vivo time-course evaluation of protein and gene knockdown in tissues (e.g., gastrointestinal tract, liver) in a simple and minimally invasive manner
- ✧ Prediction of clinical safety in humans by toxicity simulation considering the exposure of oligonucleotide therapeutics
- ✧ Prediction of toxicity based on correlation analysis technology between oligonucleotide sequences/modification and toxicity Novel gene expression control technology using oligonucleotide therapeutics, and methods to find drug targets to which the technology is applicable (oligonucleotides showing mechanisms of action other than knockdown, such as splicing control and expression enhancement)

➢ Technologies related to gene therapy (including tissue-directed vectors, tissue-specific promoters, and non-invasive administration devices)

- ✧ Selective delivery to CNS, muscles, cornea, retina, and inner ear
- ✧ Spatiotemporal regulation of gene expression, such as regulation in response to the expression of intrinsic factors and drug-induced regulation of gene expression
- ✧ Methods for evaluating immunogenicity in humans of gene therapy transgenes/proteins delivered by in vivo virus vectors
- ✧ Technologies to avoid emergence of neutralizing antibodies (including those against non-viral vectors)
- ✧ Technologies to enhance extrapolability and predictability of AAV infection to human
- ✧ Evaluation method for integration of genes into chromosomes
- ✧ Novel gene therapy technologies (RNA editing, intracellular antibodies, etc.)
- ✧ Small-volume, high-variety production methods for regenerative medicines

➢ Technologies related to targeted protein degradation

- ✧ Tissue- and/or disease-specific E3 ligases and their small molecule ligands that can be used for targeted protein degradation

- ✧ Efficient search technologies for targeted protein degradation (heterobifunctional degraders and molecular glue-type protein degraders)
- ✧ Base technologies for safety prediction of targeted protein degradation (heterobifunctional degraders and molecular glue-type protein degraders)
- ✧ Oral formulation, DDS and/or devices for medium to high molecular weight compounds (especially solubilization technology for poorly soluble medium molecular weight compounds)

➢ Drug Discovery Technologies related to small molecules that binds/interacts/modulates RNA structure or function

- ✧ Novel technologies and evaluation systems for analyzing the interaction of RNA (or RNA-protein complex) with low to medium molecular weight compounds
- ✧ Technologies to obtain small molecule compounds that bind to RNA or RNA-protein complexes and modify their functions
- ✧ Technologies to design RNA-binding drugs using isothermal titration calorimetry or thermal shift assay
- ✧ Analysis of RNA-binding proteins (comprehensive analysis method for proteins that bind to target RNA in cells)
- ✧ Synthesis technology of modified RNA (and supply of modified RNA)

➢ Other novel drug discovery technologies

- ✧ Quantitative imaging of various modalities (whole body, tissue, cell)
- ✧ Standardized biomarkers applicable for clinical trials related to diseases on this wish list (biomarkers and diagnostic agents for ALS, SLE, etc.)
- ✧ Biomarker discovery and quantification technology (liquid biopsy)
- ✧ Technology to introduce siRNA/miRNA into immune cells especially B cells (not for DDS, but for non-clinical study)
- ✧ Novel antibody generation technology for difficult targets such as GPCRs
- ✧ Technology to improve cytokine activity (modification methods to improve activity by introducing mutations)Novel chromosome incorporation technology
- ✧ Mitochondrial recombination/modification technology
- ✧ Crystal structure analysis technology by MicroED

➢ In silico analysis technology, data

- ✧ Target molecule discovery and analysis
  - Bioinformatics analysis technology (multi-omics analysis, multilayer analysis, long read sequence analysis, single cell analysis, etc.)

- Development of an algorithm to stratify new patients according to proportion of characteristic immune cell populations identified by FACS analysis of their blood cells
- Pathway analysis and building technology which has classified cases such as clinical endpoints, increase/decrease, tissue, etc. (it does not need to be quantitative)
- Pathway analysis that emphasizes not only node but also edge information
- 3D structure prediction of RNA and prediction of binding compounds

✧ Individual and organ level analysis techniques

- Pharmacokinetic prediction models for various modalities (intranasal, subcutaneous, physiologically-based pharmacokinetic, allometry, in vitro-in vivo extrapolation, drug-drug interaction)
- In silico pharmacokinetic prediction (pharmacokinetics, tissue distribution, metabolites, drug-drug interactions)
- Systems biology, systems pharmacology, mathematical modeling of CNS and immunological diseases (contract research is also available)
- Technology for creating simulation models of pathological progression of autoimmune or neurodegenerative diseases (particularly generation of virtual patients) (contract research is also available), Clinical information and its analysis

✧ Clinical information and its analysis

- Medical record containing time-series data for rare diseases such as ALS
- Medical record of muscular dystrophy containing muscular MRI data
- Omics data base such as gene expression derived from autoimmune disease patients and animal models
- Database (text data) of patients' comments and medical records
- Natural language processing technology (not just translation) for medical and life sciences that can perform at least as well in English as in Japanese
- Technology for assigning codes to medical and healthcare text data (preferably one that can automatically assign International Classification of Diseases, 10th Edition and Human Phenotype Ontology terms to some extent)

✧ Automated tools to support the creation of study reports and

pharmaceutical application documents and the confirmation of their consistency with evidence