Asahi Kasei Pharma Corporation

Asahi Kasei Pharma aims to expand and enrich the lives of people around the world through the research and development of new drugs and pharmaceutical technologies.

To achieve these goals, we have been promoting and strengthening open innovation activities worldwide. These activities include the introduction of cutting-edge technologies, partnership formation, and research collaboration. As described below, they are focused on facilitating the discovery of preclinical lead compounds and improving the efficiency of the drug development process.

We are publicly calling for new proposals related to drug development research as part its efforts for open innovation, to promote pharmaceutical research and development through enhanced cooperation with universities, research institutes, and enterprises around the world.

The application period begins on 5:00AM GMT on January 7, 2020, and ends at 8:00AM GMT on February 26, 2020.

Further information is available on Asahi Kasei Pharma's Open Innovation website:
www.asahikasei-pharma.co.jp/a-compass/en/
We look forward to receiving your proposal.

An Overview of Research Topics Sought by Asahi Kasei Pharma

- New drug candidates and drug discovery technologies in the core research fields of Asahi Kasei Pharma
  - Chronic pain, Neurodegenerative disease
  - Autoimmune disease
  - Critical care medicine
  - Bone and/or Cartilage disease
  - Muscle-related disease

- New technologies aimed at addressing the challenges in drug discovery at Asahi Kasei Pharma
  - Core technologies for drug discovery
  - Pharmacokinetics technologies
  - Formulation technologies

A detailed description of each research subject can be found in the following sections.

Contact Information: You can reach our support team using the “Contact Us” link on the web site shown above.

Research Topics Sought by Asahi Kasei Pharma

New drug candidates and drug discovery technologies in the core research fields of Asahi Kasei Pharma

<Chronic pain, Neurodegenerative disease>

1.1 New drug target molecules or new drug candidates in the field of pain management

Targeted indications: Neuropathic pain, osteoarthritic knee pain, chronic post-surgical pain, cancer pain, and lower back pain

Out of scope: Drug target molecules and drug candidates which are directly related to opioid receptors or inflammatory pathways (e.g., COX).

- Drug target molecules should be novel targets, potentially leading to the development of innovative (first-in-class) drugs. Multi-target drugs will be taken into consideration. Combination therapies fall outside of our scope.
- Proposals with in vivo data are preferable. In vivo studies using genetically modified animals are acceptable. Proposals with human studies, such as SNP analysis, are also acceptable.
- Proposals regarding drug target molecules that have already been or are being evaluated in Asahi Kasei Pharma may not be considered.

1.2 Phenotypic assay systems utilizing neuronal (e.g., dorsal root ganglia or dorsal-horn neurons) or glial (e.g., microglia or astrocytes) cells

- Proposed assay systems should be comprised of pain-related input and output units. Input/output signals related to inflammatory pain (involving, for example, NSAIDs, COX2, or prostaglandins) are outside the scope of this program.
- Proposed assay systems should be suitable for in vitro medium-throughput screening performed in a multiwell (> 96) format.
- When neuronal cells are incorporated into phenotypic assays, one of the following co-culture systems must be used to maintain the cells: a) dorsal root ganglia – dorsal-horn neurons, or b) neurons – glia cells.

1.3 Next generation technologies for drug discovery in pain research

Scope 1: Drug delivery systems to deliver small molecules into dorsal horns selectively. Proposals suitable for oral administration are preferable.

Scope 2: Technologies to generate peptides, antibodies, or proteins which can

penetrate to the central nervous system.

Scope 3: Technologies to selectively decrease the amount of target proteins in the central nervous system. Proposals suitable for small molecule drugs are preferable.

1.4 Novel drug targets, drug candidates, or drug discovery technologies for neurodegenerative diseases.

Scope 1: Novel drug targets or drug candidates for Huntington's Disease (HD), Amyotrophic Lateral Sclerosis (ALS), or spinocerebellar degeneration (SCD). Proposals with in vivo data are preferable. In vivo studies using genetically modified animals are acceptable. Proposals with human studies (such as SNP analysis) are also acceptable. Regarding ALS and SCD, sporadic ALS and multiple system atrophy (MSA), respectively, are preferable.

Scope 2: New technologies which could improve preclinical to clinical translation in the above-mentioned disease areas.

<u><Autoimmune disease></u>

2.1 A drug candidate or novel concept/idea that is applicable to the treatment of autoimmune diseases.

Proposals would contain a concept or idea that is expected to be superior to conventional therapy.

- Proposed approaches should ideally be applicable to the treatment of Systemic Lupus Erythematosus, Systemic Sclerosis, and/or Sjögren's Syndrome.
- New drug candidates must be in the preclinical stages of development.
- Proposals with specific drug candidates (small molecules, peptides, antibodies, or proteins) are preferred.

<u>< Critical care medicine ></u>

3.1 New drug target molecules or candidates for sepsis

- Proposals should achieve efficacy through activating an immune response.
- Proposals should ideally include in vivo data obtained from sepsis or infection models.

3.2 New drug target molecules or candidates for acute lung injury (ALI) or acute respiratory distress syndrome (ARDS)

3.3 New drug target molecules or candidates for severe infection including bacteremia, endocarditis, and severe pneumonia

・ Proposals should not be traditional antibiotics.

3.4 New drug target molecules or candidates for acute kidney injury (AKI)

<Bone and/or Cartilage disease>

4.1 New drug targets which are expected to provide a new therapeutic approach for rare and intractable bone diseases

・ Target indications are rare and intractable bone diseases (e.g., ossification of posterior longitudinal ligament (OPLL), fibrodysplasia ossificans progressiva (FOP), osteonecrosis, or osteogenesis imperfecta).

・ Any therapeutic modalities for drug discovery will be considered: small molecule, peptide, protein, antibody, or gene therapy, etc.

4.2 New drug discovery and development technologies which address the issues of human translation in the field of rare and intractable bone diseases

Animal models

Animal models for evaluating effects of drugs used to treat rare and intractable bone diseases such as ossification of posterior longitudinal ligament (OPLL), fibrodysplasia ossificans progressiva (FOP), osteonecrosis, or osteogenesis imperfecta.

Diagnostic modalities for drug development (e.g., biomarkers and imaging technologies for clinical and/or research uses)

A noninvasive or minimally invasive method to monitor disease progression or treatment efficacy such as:

1) blood or urine biomarkers
2) biomechanical evaluation
3) imaging technologies or analysis methods (such as CT and MRI)
   (Ideal methods should be applicable in both nonclinical and clinical settings.)

4.3 New drug candidates for rare and intractable cartilage diseases

・ Target indications are rare and intractable cartilage diseases (e.g., achondroplasia including hypochondroplasia and chondrodystrophy)

・ Any therapeutic modalities for drug discovery will be considered: small molecule, peptide, protein, antibody, or gene therapy, etc.

4.4 New technologies to enhance the efficacy of conventional surgical treatments such as microfracture and cell therapy for articular cartilage injury or degeneration

・ New drug candidate compounds and/or biomaterials including membranes, glues and scaffolds will be considered.
・ The proposed compounds or biomaterials are required to enhance the regeneration of normal cartilage tissue through the promotion of cell recruitment or engraftment at application sites and stay in the lesions after articular injection or arthroscopic surgery.

<Muscle-related disease>

5.1 New drug targets or drug seeds in muscle-related diseases

・ Target indications are Sarcopenia, Cancer cachexia, Muscle disuse atrophy, and refractory muscle diseases (e.g. muscular dystrophy, myasthenia gravis, etc.).
・ Drug target molecules that are highly novel and beneficial, and can be innovative new drugs (first-in-class) are desirable.
・ Drug target molecules that can increase muscle mass and muscle strength, and enhance muscle performance based on the concept of senescence inhibition/aging control, such as the removal of senescence cells or the NAD+/Sirtuin pathway activation, either of which affects to increase muscle mass/strength, or longevity-regulatory factors which potentially affect to increase in muscle mass/strength are desirable.
・ Target tissues and organs are not limited to muscle. Drug target molecules that can be therapeutics to muscle-related diseases acting on muscle even if it is secondary effect are also appropriately evaluated. However, anti-cancer drugs to cancer cachexia is out of scope.
・ Drug target molecules/drug seeds validated by in vivo data (analysis using gene-deficient mice are acceptable) are desirable. Drug target molecules/drug seeds with evidence in human such as SNPs are also welcomed.

<Core technologies for drug discovery>

6.1 Isotope-labeling technique for interaction analysis by solution-state NMR spectroscopy of water-soluble proteins or integral membrane proteins

larger than 40-kDa

Your technique must meet requirement A or B below.

A: Deuteration technique which does not decrease protein-expression level.

B: Labeling technique which exhibits sensitivity and resolution equal to or higher than deuterium labeling.

- You may choose any host cells for recombinant expression; such as E. coli, Pichia pastoris, insect cells and mammalian cells.
- Selective labeling or incorporation of unnatural amino acids is acceptable.
- Post-expression labeling is not eligible for this recruitment.
- You must provide the acquisition parameters suitable for the proposed labeling technique.

6.2 Technologies to improve the membrane permeability of functional peptides for their intracellular delivery

- Intracellular activity should be validated by pharmacological output other than cell viability assays.
- Peptide size should be less than 40 amino acids.

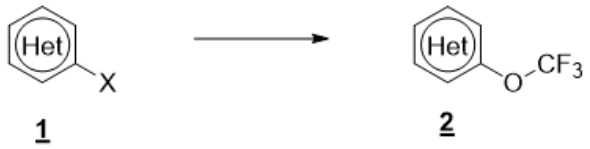
6.3 Techniques to discover small-molecular drug candidates based on the cocrystal structure of the target protein and its peptide ligand

Example: Structure-based drug design by in silico screening and/or chemical substitutions of the (downsized) peptide structures

6.4 One-step synthesis of OCF_3 group incorporating heteroaromatic compounds.

The reaction must meet the following requirements:

- Direct conversion using halogens or other functional groups.
- Using pyridine derivatives or other pharmaceutical intermediates as a starting material.



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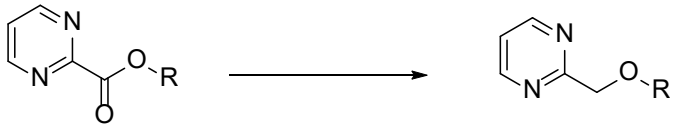
X=Cl, Br, I, etc.

6.5 A practical reaction for ether synthesis based on the reduction of pyrimidine-2-carboxylate derivatives.

The reaction conditions must be suitable for scale-up synthesis.

- mild reaction conditions
- simplified procedure and work-up method
- reasonably priced reagents



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R = alkyl

<Pharmacokinetics technologies>

7.1 Technologies for measuring endogenous biomarkers that can precisely predict pharmacokinetic drug interactions

Example: a) Novel endogenous biomarkers, b) Techniques to improve the measurement sensitivity of existing endogenous biomarkers

- It is desirable that the molecule be detectable in plasma or urine samples.
- Molecules that cannot be measured by LC-MS/MS or are observed only in rodents will not be accepted as targets.

7.2 In vivo technologies to precisely evaluate CNS penetration

Example: a) Correction technique for concentration in the brain using blood brain barrier impermeability marker, especially for low CNS-permeable drugs

- Techniques that can be evaluated by oral administration are preferred.
- Technologies that require imaging MS or radioactive materials will not be accepted as targets.

7.3 Efficient methods for analyzing the pharmacokinetics of peptides

Example: a) Technology for low-cost/short-term 14C-labeling of unnatural amino acids, except for terminal methylation, b) In silico technology for predicting metabolically unstable sites of peptides containing non-native amino acids.

- Improvement of existing technology, and development of a new technique or software are included in the scope of the project, but use of imaging mass

spectrometry will not be accepted.

- Technologies that can reduce cost and time compared with existing ones are preferable.

<Formulation technologies>

8.1 Novel techniques for stabilizing peptide- and protein-based drugs in aqueous solutions

Applications proposing to use the following approaches will not be considered:

- Lyophilization
- Any procedures that prevent the subcutaneous injection of the drugs
- Covalent modification of the drugs

8.2 New technologies for the sustained release of peptides and proteins

Proposals should ideally include in vivo data.

Proposed technologies must meet the following three requirements:

- Controlled release has been shown to continue for at least four weeks.
- Proposed methods should be clearly superior to existing techniques.
- Proposed methods should be compatible with subcutaneous administration.

8.3 Technologies to improve oral absorption or persistent blood concentration of peptide drugs

Example: a) Techniques to achieve more than 10% oral bioavailability with peptide drugs, b) Technologies to retain significant blood levels of peptide drugs for at least several days after administration

- Modification to the chemical structure (e.g. prodrug), drug formulation, or minimally invasive devices are included in the scope.
- Technologies with which preliminary in vivo data have been obtained are preferable.