

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 3:00 a.m. GMT on January 7, 2019, and ends at 8:00 a.m. GMT on February 22, 2019.

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 development technologies in the core research fields of Asahi Kasei Pharma
 - Chronic Pain
 - Autoimmune Diseases
 - Critical Care Medicine
 - Bones and Cartilage
- New technologies aimed at addressing the challenges in drug discovery and development at Asahi Kasei Pharma
 - Drug Development Core Technology

- Prediction of Pharmacokinetics and Toxicity
- Drug Manufacturing Technology
- Identification of novel drug indications

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 Request for Proposal page shown above.

Research Topics Sought by Asahi Kasei Pharma

- **New drug candidates and drug development technologies in the core research fields of Asahi Kasei Pharma**

Chronic Pain

<Drug Candidates>

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

- Our scope of indication: Neuropathic pain, osteoarthritic knee pain, postoperative pain, and cancer pain
- Out of our scope: Drug-target molecules and drug candidates that directly act on opioid receptors or inflammatory pathways (e.g., COX)
 - a) Drug targets should ideally be novel molecules, potentially leading to the development of innovative (first-in-class) drugs. We will consider proposals involving multi-target drugs. Combinatorial therapies fall outside the scope of this program announcement.
 - b) Proposals should ideally provide in vivo data. (In vivo studies with relevant knockout mice are also acceptable.) Proposals with evidence from human studies (such as SNP analysis) will also be considered.
 - c) Proposals concerning drug-target molecules that have already been or are being evaluated in Asahi Kasei Pharma may not be considered.

<Drug Development Technologies>

1.2 New animal models of pain or new techniques for pain measurement that could be useful from the viewpoint of translational research

Specifically, we are interested in the following:

- New models of chronic pain or new pain assessment methodologies that utilize non-human primates
- New models of diabetic neuropathy or its bioassay systems that utilize rodents

1.3 Simple and reproducible electrophysiological techniques for in vivo evaluation including analysis of drug candidates during non-clinical studies (The analysis must use rodents or higher mammals.)

Examples: A technique that can quantify pain-induced neuronal firing (activity) without surgery. (Minor procedures for inserting electrodes into living tissue such as the spinal cord could be acceptable)

1.4 Technologies to differentiate human iPS cells into dorsal root ganglia, dorsal-horn neurons, or glial cells (microglia or astrocytes)

- Differentiated cells should possess the functional characteristics of their corresponding primary cultures. The characteristics include expression patterns of marker genes/proteins, profiles of cellular responsiveness, and activities of reference compounds.
- Proposed technologies should allow for the robust and reproducible production of differentiated cells for in vitro screening in multiwell (> 96) plates.

1.5 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 announcement.
- 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: 1) dorsal root ganglia and dorsal-horn neurons, or 2) neurons and glia.

1.6 Verified biomarkers related to therapeutic effect or disease progression of neuropathic pain in humans (patients) and animal models

Autoimmune Diseases

<Drug Candidates>

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

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

- New drug candidates must be in the stage from basic research to preclinical development.
- Proposed approaches should ideally be applicable to the treatment of rheumatoid arthritis.
- Proposals with specific drug candidates (small molecules, peptides, antibodies, or proteins) are preferred.

Critical Care Medicine

<Drug Candidates>

3.1 New drug candidates for treating sepsis by activating immune responses

- Proposals should ideally include in vivo data obtained from sepsis or infection models. (Laboratory animals injected with LPS will not be considered.)

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

Bones and Cartilage

<Drug Development Technologies>

4.1 New drug discovery technologies which address the issues of human translation in the field of bone regenerative medicine

4.1.1. Animal models

- Animal models for evaluating the regenerative effects of drugs used to treat refractory bone diseases, such as osteonecrosis and long bone fractures with non-union or delayed healing

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

- A noninvasive or minimal invasive method to monitor a disease progression or an efficacy of treatment such as a) blood or urine biomarkers b) biomechanical evaluation , and c) imaging technologies or analysis methods (such as CT and MRI).
(Ideal methods should be applicable in both nonclinical and clinical settings.)

4.2 New technologies for drug discovery that directly address clinical needs in the field of cartilage regenerative medicine

4.2.1. In vitro assay systems or animal models

- In vitro assay systems to evaluate regenerative effects of drugs or cells on articular cartilage degeneration or intervertebral disc degeneration:
Examples) Co-cultures of graft cells with isolated animal cartilage cells.
Cartilage organ culture systems.
- Animal models to evaluate regenerative effects of drugs or cells on articular cartilage degeneration (OA, TA) or intervertebral disc degeneration:
Laboratory animals that can potentially be used for these models include rats, miniature pigs, rabbits, and monkeys.
(Ideal models should allow for the long-term assessment of human cell-based treatment under immunosuppressive conditions.)

4.2.2. Diagnostic modalities for drug development (e.g., biomarkers and imaging technologies)

- Techniques for tracking disease progression or therapeutic response in a noninvasive or minimally invasive manner: a) blood or urine biomarkers, b) biomechanical measurement devices, and c) imaging technologies and image analysis tools (such as CT and MRI).
(Ideal methods should be applicable in both nonclinical and clinical settings.)

● New technologies aimed at addressing the challenges in drug discovery and development at Asahi Kasei Pharma

Drug Development Core Technologies

5.1 Novel techniques for performing structural analysis with crystalline sponges, and new approaches for constructing these molecular cages for the structure determination of low-size molecular (MW $\geq$ 500) and middle-size molecular (peptide) compounds

- Proposed crystalline sponges should ideally be able to accept a wide range of guest compounds (e.g., both polar and nonpolar molecules).
Alternatively, multiple molecular cages could be built to accommodate a large number of different guest molecules with varying physical properties.

5.2 Highly accurate computational method for predicting the acid dissociation constant (pKa) of a small molecule

- Machine learning approaches will not be considered.

5.3 A new algorithm for the accurate modeling of membrane proteins (particularly ion channels)

- The performance of the algorithm must have been validated with membrane proteins other than GPCR.

5.4 Reaction prediction using a quantum chemistry computational method

- A new methodology for precisely simulating reaction pathways.
- Ideally, proposed approaches should be made readily accessible to chemical scientists.
- AI-based reaction prediction will not be considered.

5.5 New descriptors of chemical compounds for the precise modeling of quantitative structure-activity relationships

5.6 A new computational approach to predict protein-ligand binding kinetics (kon/koff)

5.7 New technology of photoredox reaction for scaling up

- Proposed technologies or devices must be able to scale up for several tens of grams.
- After scaling up the reactions, the yield must be similar to published data.
- The batch reaction systems that can readily be performed in our laboratory will be high priority. The use of a high-cost device (multimillion US dollars) will not be considered.

Prediction of Pharmacokinetics and Toxicity

6.1 A new technology enabling the effective oral delivery of middle size-molecules including cyclic peptides

6.2 In vitro or in silico methodology elucidating the clearance mechanisms including proteolytic elimination and target-mediated drug disposition of middle size-molecules, e.g. cyclic peptides

6.3 In silico technologies for predicting on-target toxicities of drug-target proteins

- Can be utilized for the go/no-go decision or prioritization of potential drug-target proteins.
- Applies pathway (or mapping) analysis techniques created based on gene expression, protein-protein interaction, [and/or] text mining.
- Includes the datasets or model built from multiple publicly-available databases.

Pharmaceutical Technologies

7.1 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

7.2 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.

Identification of Novel Drug Indications

8.1 Discovery of new indications for secreted frizzled-related protein 1 (sFRP1) inhibitors

- Chemical compounds developed at Asahi Kasei Pharma will be provided at no cost. (Their structural information will not be disclosed.)
- The characteristics of our compounds:
 - a) Have approximately 50-fold higher sFRP1-inhibition activities, as compared with the commercially-available tool compound, WAY-316606.

- b) Can be administered orally.
- High priority will be given to research projects that focus on the field of orthopedics, the medical field where Asahi Kasei Pharma directs its research and development efforts. (Proposals involving osteoporosis research will not be considered.)

8.2 Discovery of new indications for transient receptor potential ankyrin 1 (TRPA1) inhibitors in the field of orthopedics

- A chemical compound developed at Asahi Kasei Pharma will be provided at no cost. (Its structural information will not be disclosed.)
- The characteristics of our compound:
 - a) Can inhibit both human and rat TRPA1 with an IC50 value at a few nanomolar.
 - b) Can be administered orally.
- Target indications should belong to the group of orthopedic disorders. (Proposals involving pain will not be considered.)