Astellas is efficiently advancing research and development by building systems to continuously create innovative medicines, along with challenging new opportunities, including new therapeutic areas and technologies.

**Gilteritinib**

Gilteritinib is a FLT3/AXL inhibitor which is being developed for acute myeloid leukemia (AML). Gilteritinib inhibits both FLT3, a receptor-type tyrosine kinase known to be involved in cancer cell proliferation, and AXL which is reported to be associated with resistance to some forms of chemotherapy. Considering the five-year survival rate for AML estimated to be approximately 25%*, the arrival of a promising new treatment has been awaited. The clinical data obtained so far suggested the efficacy and safety of gilteritinib in patients with FLT3 mutations who are known to have poor prognosis. Astellas is exploring a potential of gilteritinib in a broad range of the treatment paradigm for AML.

Astellas is currently conducting multiple Phase 3 trials including ADMIRAL study in relapsed or refractory FLT3-positive AML patients, which is the most difficult AML patient segment to treat. Gilteritinib has been granted for SAKIGAKE designation in Japan. Astellas is working to further reduce the total development period by allocating resources to gilteritinib as a prioritized project.

* NIH, National Cancer Institute, Cancer Stat Facts, Acute Myeloid Leukemia (AML)

**Enfortumab Vedotin**

Enfortumab vedotin is an antibody drug conjugate (ADC) targeting Nectin-4, a cell adhesion molecule. While it is stable in blood, it is designed to kill only the targeted cancer cells after it is internalized into cancer cells expressing Nectin-4.

In urothelial cancer, a target indication of enfortumab vedotin, it is reported that some patients are confirmed for metastasis at the time of initial diagnosis and the five-year survival rate is low. A high relapse rate is reported even if diagnosed and treated at an early stage. A promising new treatment is awaited.

Currently, Phase 2 trial in patients previously treated with checkpoint inhibitor (CPI) therapy is under preparation.

**Research Initiatives**

In the oncology field, the interest to cancer immunotherapy targeting immune checkpoints has been increasing recently. On the other hand, it has been pointed out that immune checkpoint inhibitors are ineffective for certain types of cancer and a segment of the patient population. Astellas believes that immuno-oncology is a strategically important approach.

As one of the initiatives in this therapeutic area, Astellas launched a partnership with Potenza Therapeutics, Inc. in 2015. To address the cancer types which do not respond to the current cancer immunotherapy, Astellas is pursuing research and development of a next-generation cancer immunotherapy with different targets than current treatments. Two programs are underway to enter into the clinical development phase.
Roxadustat is a hypoxia-inducible factor (HIF) prolyl hydroxylase (PH) inhibitor with oral administration. Astellas is developing roxadustat for anemia associated with chronic kidney disease (CKD) in dialysis and non-dialysis. For filing and reimbursement in the EU, a total of six Phase 3 studies are being conducted. Another six Phase 3 studies are being conducted in Japan.

Anemia is one of the common complications of CKD. It is said that the progression of anemia in CKD leads to end-stage renal disease and increases the mortality rate. Therefore, monitoring the hemoglobin (Hb) levels in patients with anemia in CKD is a crucial issue in the treatment of renal dysfunction.

Roxadustat is thought to increase HIF, which is involved in the production of red blood cells, by inhibiting HIF-PH, thereby enhancing the production of red blood cells and improving anemia.

Roxadustat has a different mechanism of action than conventional treatments and can be administered orally. It is thus expected to become a new treatment option which could provide both effectiveness and convenience for patients.

ASP8232

ASP8232 is a VAP-1 inhibitor being developed for diabetic nephropathy. Astellas has obtained the results of Phase 2 trial and is preparing for a subsequent trial.

Diabetic nephropathy is one of major underlying diseases for dialysis treatment. It is a common complication of diabetes. It is said that around half of patients suffering from diabetes for more than 20 years associate with diabetic nephropathy. With existing treatment methods limited to dialysis and kidney transplantation, there is a need for a new treatment.

Urology and Nephrology

**Roxadustat**

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**TOPIC** IMAB362

**Acquisition of Late-Stage Development Compound in Oncology**

Oncology is one of the important franchises that will drive the growth of Astellas. Through the acquisition of Ganymed Pharmaceuticals AG, Astellas has acquired multiple oncology pipeline assets in pre-clinical and clinical stages including IMAB362, which is being developed for the indication of gastroesophageal adenocarcinoma.

IMAB362 is an antibody targeting Claudin 18.2, a transmembrane protein that forms a tight junction connecting and binding membranes of two adjoining cells. Claudin 18.2 is expressed locally in stomach cells for normal cells. Claudin 18.2 is expressed in various cancers, 80% in gastrointestinal adenocarcinomas and 60%* in pancreatic, biliary duct, ovarian and lung cancer.

Phase 2b clinical trial (FAST) of IMAB362 showed that IMAB362 extended the median progression-free survival and the median overall survival. In the patient subgroup with high expression levels of Claudin 18.2, IMAB362 group resulted in nearly doubling the overall survival compared with the control group. The most frequent adverse events observed during the study were vomiting, nausea and neutropenia.

Astellas is preparing for Phase 3 trial of IMAB362. Through this acquisition, Astellas will further strengthen its oncology franchise.

* Al-Batran et al., 2016 American Society of Clinical Oncology
ASP0113 is a DNA vaccine being developed as a treatment to prevent cytomegalovirus (CMV) infection in hematopoietic cell transplant (HCT) patients. Currently, Astellas is conducting Phase 3 trial of ASP0113 in HCT patients.

CMV infection and CMV reactivation are opportunistic infections commonly observed after hematopoietic cell transplantation and potentially lead to death in severe cases. From the standpoint of strengthening the control of infections, a prophylactic vaccine without safety concern is anticipated.

ASP0113 builds immunity to CMV-derived antigen proteins by expressing CMV-derived antigen proteins in the body and inducing both cellular and humoral immune responses. ASP0113 is expected to suppress CMV infection and complications associated with CMV infection after hematopoietic cell transplantation.

Peficitinib

Peficitinib is a JAK inhibitor being developed for rheumatoid arthritis. Phase 3 clinical trials are currently being conducted in Japan. Astellas expects to obtain the results of these trials within fiscal year 2017. Rheumatoid arthritis is a chronic inflammatory autoimmune disease due to an immune disorder. The current standard treatments for rheumatoid arthritis are biologics including TNF-α drugs.

Peficitinib has a different mechanism of action than other immunosuppressants. Peficitinib is thus expected to be a new drug treatment option which could be safe and convenient for patients.

DNA Vaccine Using LAMP-vax Technology

LAMP-vax technology is expected to serve as a drug discovery platform for creating drug products aimed for treatment or prophylaxis of a wide range of allergic diseases by enhancing the therapeutic effectiveness of DNA vaccines and changing the types of allergens encoded in plasmid DNA. Multiple development compounds using LAMP-vax technology are currently in non-clinical and clinical stages.

Phase 1 trial of ASP0892 is currently being conducted in the U.S. targeting peanut allergy, and it has been granted Fast Track designation by the Food and Drug Administration (FDA). Peanut allergy can be a fatal food-related allergy with potential of life-threatening anaphylaxis induced by trace exposure. There is no currently approved treatment and prophylaxis drugs for peanut allergy.

Astellas is developing ASP4070 targeting allergies induced by Japanese red cedar pollen. Phase 2 trial of ASP4070 has been initiated in Japan in 2017. It is said that about one in four Japanese people suffer from allergies to Japanese red cedar pollen. The currently available treatment is mainly symptomatic treatments. ASP4070 is expected to become a fundamental treatment that will relieve allergy symptoms or achieve symptomatic remission over the long term with only a short-term administration.

Drug Discovery Platform Using LAMP-vax Technology

<table>
<thead>
<tr>
<th>Food allergy</th>
<th>Seasonal pollen allergy</th>
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<td>ASP0892 for peanut allergy</td>
<td>ASP4070 for pollinosis caused by Japanese red cedar</td>
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<tr>
<td>P1 study</td>
<td>P2 study</td>
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</table>

Perennial allergy
Pre-clinical
e.g. house dust mite, cat, etc.

Research Initiatives

In immunology, Astellas is working to develop an innovative drug discovery platform that will enable antigen-specific immune control. Astellas is also researching safe and fundamental treatments for allergies, autoimmune diseases, and infectious diseases. With regard to autoimmune diseases for which the specific antigens have been identified, through joint research with Kanyos Bio, Inc., Astellas has begun research that applies unique technologies for the induction of antigen-specific immune tolerance using red blood cells. For diseases in which specific organs are impaired by the excessive responses of immune systems due to specific antigens, regardless of whether the condition involves the body’s autoimmune or non-autoimmune systems, Astellas is promoting research and development activities using a unique technology targeting red blood cells that induces immune tolerance by removing T cells that cause excessive antigen-specific responses.
AIRM (Company name was changed after acquisition of Ocata Therapeutics, Inc.) possesses the world’s highest level of technology and expertise in research and development capabilities of cell therapy, taking a leading position in this field. AIRM seeks to realize cutting-edge drug discovery based on leading cell therapy approaches, thereby contributing to ophthalmology treatments with high unmet medical needs.

Currently, AIRM is promoting development activities targeting age-related macular degeneration and Stargardt macular degeneration with a focus on retinal pigment epithelium (RPE) cells, which are vital to the survival of visual cells and the maintenance of their functions. For both diseases, it is currently in the Phase 2 trial stage.

In the muscle diseases area, CK-2127107, a fast skeletal troponin activator, has entered the clinical stage. Astellas is currently proceeding with Phase 2 trials for three diseases related to the atrophy of skeletal muscles: spinal muscular atrophy, amyotrophic lateral sclerosis, and chronic obstructive pulmonary disease. Of those three diseases, the trial targeting spinal muscular atrophy is in the most advanced clinical stage. Spinal muscular atrophy is a serious disease in which the progression of muscular atrophy can trigger respiratory failure and motor impairment. Astellas is working to provide a new treatment option for these diseases.

In addition, Astellas is steadily proceeding with preparations to initiate clinical trials of MTB-1, a mitochondrial gene expression regulator, including convening an advisory meeting of a neuromuscular disease committee. MTB-1 is a development candidate under collaboration with Mitobridge, Inc.

**New Therapeutic Areas and Others**

**Astellas Institute for Regenerative Medicine (AIRM)**

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**TOPIC**

**Fezolinetant**

**Anticipated to Provide a New Treatment Option to Replace Current Hormone Replacement Therapy**

Through the acquisition of Ogeda SA, Astellas obtained fezolinetant, a selective NK3 antagonist currently being developed for menopause-related vasomotor symptoms (VMS: hot flashes and night sweats). Astellas is currently conducting Phase 2b trial of fezolinetant.

It is reported that MR-VMS is recognized in nearly 80%* of post-menopausal women. Given that existing hormone replacement treatments present safety concerns, a safe and effective non-hormonal therapy is awaited as a new treatment option. In a Phase 2a study, fezolinetant showed good results in terms of improvement in the frequency and extent of hot flashes. Based on these results, Astellas expects fezolinetant to become a first-in-class, non-hormonal treatment for MR-VMS.

Astellas has built up strengths through the development of many small molecule drugs that improve patients’ quality of life, including treatments in the OAB area and promoting the development of fezolinetant to provide a new treatment option to the patients with MR-VMS. In addition, since both MR-VMS and OAB affect middle-aged and elderly women, Astellas expects to capture synergies with its strengths in the OAB area which have been developed over the years.

* UpToDate – Clinical manifestations and diagnosis of menopause (Literature review current through June 2017)