Profiles of Major Products under Development (As of January 28, 2021)

1. Psychiatry & Neurology

**SEP-363856**
Origin: in-house (Joint research with Sunovion Pharmaceuticals Inc. and PsychoGenics Inc.), Formulation: oral
- SEP-363856 is an antipsychotic agent with a novel mechanism of action, a TAAR1 (trace amine-associated receptor 1) agonist with serotonin 5-HT\textsubscript{1A} agonist activity and doesn't bind to dopamine D\textsubscript{2} or serotonin 5-HT\textsubscript{2A} receptors. Sunovion discovered SEP-363856 in collaboration with PsychoGenics using its in vivo phenotypic SmartCube\textsuperscript{®} platform and associated artificial intelligence algorithms. Phase 2 results in patients with schizophrenia support the efficacy of SEP-363856 in treating both positive and negative symptoms of schizophrenia, while demonstrating a side effect profile with notable similarities to placebo: extrapyramidal symptoms, weight gain, lipid and glucose derangements or prolactin elevation.
- Development stage:
  - Schizophrenia: Phase 3 in the U.S.
  - Parkinson’s disease psychosis: Phase 2 in the U.S.
  - Schizophrenia: Phase 1 in Japan

**vatiquinone (EPI-743)**
Origin: PTC Therapeutics, Inc. (Acquired from BioElectron Technology Corporation), Formulation: oral
- EPI-743 is expected to show efficacy by removing the oxidative stress that is generated excessively by decreased mitochondrial function. It is expected to be the world’s first treatment for mitochondrial diseases, beginning with Leigh syndrome, for which there is no effective therapy.
- Development stage:
  - A Phase 2 / 3 study for Leigh syndrome in Japan completed, development strategy under consideration

**EPI-589**
Origin: PTC Therapeutics, Inc. (Acquired from BioElectron Technology Corporation), Formulation: oral
- EPI-589 is expected to show efficacy by removing the oxidative stress that is generated excessively by decreased mitochondrial function. It is expected to be developed for neurodegenerative indications arising through redox stress.
- Development stage:
  - Parkinson’s disease: Phase 2 in the U.S.
  - Amyotrophic lateral sclerosis (ALS): Phase 2 in the U.S.
  - Amyotrophic lateral sclerosis (ALS): Phase 1 in Japan

**SEP-4199**
Origin: in-house (Sunovion Pharmaceuticals Inc.), Formulation: oral
- SEP-4199 is a non-racemic ratio of amisulpride enantiomers. Sunovion discovered that the pharmacology of amisulpride is enantiomer-specific, and that increasing the ratio of R-amisulpride to S-amisulpride increases the potency for serotonin 5-HT\textsubscript{7} receptors relative to dopamine D\textsubscript{2} receptors. SEP-4199 was designed with an 85:15 ratio of R-amisulpride to S-amisulpride to increase levels of serotonin 5-HT\textsubscript{7} activity intended to enhance antidepressant efficacy and produce reduced levels of D\textsubscript{2} receptor occupancy appropriate for the treatment of bipolar depression.
- Development stage:
  - Bipolar I depression: Phase 2 in the U.S. and Japan
DSP-6745  Origin: in-house, Formulation: oral
- DSP-6745 is a serotonin 5-HT$_2A$ and serotonin 5-HT$_2C$ receptors dual antagonist, which is expected to be effective for Parkinson's disease psychosis and one or more Parkinson's disease non-motor symptoms (depression, anxiety, or cognitive impairment). In addition, DSP-6745 has negligible affinity for dopamine D$_2$ receptors.
- Development stage: Parkinson's disease psychosis: Phase 1 in the U.S.

SEP-378608  Origin: in-house (Joint research with Sunovion Pharmaceuticals Inc. and PsychoGenics Inc.), Formulation: oral
- SEP-378608 is a novel CNS-active molecule. Sunovion discovered SEP-378608 in collaboration with PsychoGenics using its in vivo phenotypic SmartCube® platform and associated artificial intelligence algorithms. Pre-clinical studies suggest that it may modulate neuronal activity in key areas of the brain associated with the regulation of mood.
- Development stage: Bipolar disorder: Phase 1 in the U.S.

DSP-3905  Origin: in-house, Formulation: oral
- DSP-3905 is an agent that selectively inhibits voltage-gated sodium channels Nav1.7. Based on its inhibitory mode of action, the agent is expected to show a potent analgesic effect on the pain occurring when neurons get excessively excited. In addition, DSP-3905 has a high selectivity for Nav1.7 expressed in peripheral neuron and may not produce central nervous system or cardiovascular system side effects, which are present with the current drugs for neuropathic pain.
- Development stage: Neuropathic pain: Phase 1 in the U.S.

SEP-378614  Origin: in-house (Joint research with Sunovion Pharmaceuticals Inc. and PsychoGenics Inc.), Formulation: oral
- SEP-378614 is a novel CNS-active molecule. Sunovion discovered SEP-378614 in collaboration with PsychoGenics using its in vivo phenotypic SmartCube® platform and associated artificial intelligence algorithms. Pre-clinical studies suggest that it may have rapid onset and long lasting antidepressant-like activity and enhance neuroplasticity.
- Development stage: Treatment resistant depression: Phase 1 in the U.S.

SEP-380135  Origin: in-house (Joint research with Sunovion Pharmaceuticals Inc. and PsychoGenics Inc.), Formulation: oral
- SEP-380135 is a novel CNS-active molecule. Sunovion discovered SEP-380135 in collaboration with PsychoGenics using its in vivo phenotypic SmartCube® platform and associated artificial intelligence algorithms. Pre-clinical studies showed a broad range of in vivo activities suggesting efficacy against a number of behavioral and psychological symptoms in dementia, including agitation/aggression, psychomotor hyperactivity, depression and deficits in social interaction.
- Development stage: Agitation in Alzheimer's disease: Phase 1 in the U.S.

DSP-1181  Origin: in-house, Formulation: oral
- DSP-1181 is a novel compound created by Sumitomo Dainippon Pharma using Exscientia's AI technologies. In contrast to conventional serotonin 5-HT$_1A$ receptor partial agonists (non-benzodiazepine anxiolytics), DSP-1181 has a potent full agonistic activity for serotonin 5-HT$_1A$ receptors and is expected to have a long half-life, and therefore it is suggested that DSP-1181 has strong efficacy over a long period of time. In obsessive compulsive disorder (OCD) model mice manipulated OCD-related neural circuit, DSP-1181 is expected to have an earlier onset of efficacy than a standard medication, a selective serotonin reuptake inhibitor (SSRI).
- Development stage: Obsessive compulsive disorder: Phase 1 in Japan.
2. Oncology

napabucasin (BBI608)  
Origin: in-house (former Boston Biomedical, Inc.), Formulation: oral

- BBI608 is an orally administered small molecule agent with a novel mechanism of action that is bioactivated by the enzyme NQO1 in cancer cells, which generates reactive oxygen species (ROS) to inhibit cancer stemness and tumor progression-related pathways including STAT3, which is expected to result in cancer cell death.

- Development stage:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Proposed indication</th>
<th>Country/Area</th>
<th>Combination products</th>
<th>Study number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3</td>
<td>Colorectal cancer (combination therapy)</td>
<td>U.S., Japan</td>
<td>FOLFIRI(^3), FOLFIRI(^3) + bevacizumab</td>
<td>CanStem303C</td>
</tr>
<tr>
<td>Phase 1/2</td>
<td>Solid tumors(^1) (combination therapy)</td>
<td>U.S.</td>
<td>paclitaxel</td>
<td>201</td>
</tr>
<tr>
<td></td>
<td>Hepatocellular carcinoma(^2) (combination therapy)</td>
<td>U.S.</td>
<td>sorafenib</td>
<td>HCC-103</td>
</tr>
<tr>
<td></td>
<td>Solid tumors (combination therapy)</td>
<td>U.S.</td>
<td>ipilimumab, pembrolizumab, nivolumab</td>
<td>201CIT</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal cancer (combination therapy)</td>
<td>U.S., Canada</td>
<td>FOLFIRI(^3), FOLFIRI(^3) + bevacizumab, CAPOX(^3), FOLFIRI(^3), FOLFIRI(^3) + bevacizumab, regorafenib, irinotecan</td>
<td>246</td>
</tr>
</tbody>
</table>

\(^*\)1 Phase 2 stage: Ovarian cancer, Breast cancer, Melanoma, etc.
\(^*\)2 Phase 2 stage
\(^*\)3 FOLFOX: Combination therapy with fluorouracil, leucovorin, oxaliplatin
CAPOX: Combination therapy with capecitabine, oxaliplatin
FOLFIRI: Combination therapy with fluorouracil, leucovorin, irinotecan

alvocidib (DSP-2033)  
Origin: Sanofi S.A., Formulation: injection

- Alvocidib is a small molecule inhibitor of cyclin-dependent kinase 9 (CDK9), a member of cyclin-dependent kinase family, which activates transcription of cancer-related genes. The subsequent down-regulation of MCL-1, an anti-apoptotic gene, may be responsible for the potential clinical anti-cancer activity observed with alvocidib.

- Development stage:

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<tbody>
<tr>
<td>Phase 2</td>
<td>Acute myeloid leukemia (monotherapy/combo therapy) (refractory or relapsed patients following treatment with venetoclax combination therapy)</td>
<td>U.S.</td>
<td>cytarabine</td>
<td>TPI-ALV-202</td>
</tr>
<tr>
<td>Phase 1/2</td>
<td>Myelodysplastic syndromes (combination therapy)</td>
<td>U.S.</td>
<td>decitabine, azacitidine</td>
<td>TPI-ALV-102 (Zella 102)</td>
</tr>
</tbody>
</table>

adegramotide/nelatimotide (DSP-7888)  
Origin: in-house, Formulation: injection

- DSP-7888 is a therapeutic cancer peptide vaccine derived from Wilms’ tumor gene 1 (WT1) protein. DSP-7888 is a vaccine containing peptides that induces WT1-specific cytotoxic T lymphocytes (CTLs) and helper T cells. DSP-7888 is expected to become a treatment option for patients with various types of hematologic malignancies and solid tumors that express WT1 by inducing WT1-specific CTLs that attack WT1-expressing cancer cells. By adding a helper T cell-inducing peptide, improved efficacy over that observed with a CTL-inducing peptide alone may be achieved. DSP-7888 is expected to be an option for a wide range of patients.
Profiles of Major Products under Development

<table>
<thead>
<tr>
<th>Stage</th>
<th>Proposed indication</th>
<th>Country/Area</th>
<th>Combination products</th>
<th>Study number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2</td>
<td>Glioblastoma (combination therapy)</td>
<td>U.S., Japan</td>
<td>bevacizumab</td>
<td>BBI-DSP7888-201G</td>
</tr>
<tr>
<td>Phase 1/2</td>
<td>Solid tumors (combination therapy)</td>
<td>U.S.</td>
<td>nivolumab, pembrolizumab</td>
<td>BBI-DSP7888-102CI</td>
</tr>
</tbody>
</table>

**dubermatinib (TP-0903)**  
- **Origin:** University of Utah, **Formulation:** oral
- TP-0903 is an inhibitor of multikinase including AXL receptor tyrosine kinase inhibitor, which is known to be involved in acquiring resistance to conventional agents and developing metastatic capacity in cancer cells. TP-0903 may have anti-cancer activities on various cancer types through blocking transition from epithelial to mesenchymal phenotype by inhibiting AXL. TP-0903 has been shown to inhibit AXL signaling and reverse the mesenchymal to epithelial phenotype in pre-clinical studies.
- **Development stage:**
  - Solid tumors (monotherapy / combination therapy): Phase 1 in the U.S. and Japan

**DSP-0509**  
- **Origin:** in-house, **Formulation:** injection
- DSP-0509 is a novel Toll-like receptor (TLR) 7 agonist. DSP-0509 may promote the cytokine induction and cytotoxic T lymphocyte (CTL) activation mediated by agonistic effect of TLR 7 expressing in plasmacytoid dendritic cell. Furthermore, DSP-0509 is expected to sustain the immune-mediated anti-cancer activity by induction of immune system memory T cells.
- **Development stage:**
  - Solid tumors (monotherapy / combination therapy): Phase 1/2 in the U.S.

**TP-0184**  
- **Origin:** in-house (former Tolero Pharmaceuticals, Inc.), **Formulation:** oral
- TP-0184 has an inhibitory effect against kinase such as ALK2 and ALK5, part of the transforming growth factor beta (TGFβ) receptor superfamily. In myelodysplastic syndromes, the ALK5 pathway is activated and caused abnormal erythroid differentiation. TP-0184 is expected to show anti-cancer activities through the kinase inhibitory effect.
- **Development stage:**
  - Anemia associated with myelodysplastic syndromes (monotherapy): Phase 1/2 in the U.S.
  - Solid tumors (monotherapy): Phase 1 in the U.S.

**DSP-0337**  
- **Origin:** in-house, **Formulation:** oral
- DSP-0337 is a small molecule oral prodrug of napabucasin. DSP-0337 is expected to be stable and dispersed in the stomach, and converted to napabucasin in the intestine, which may be absorbed and exert its pharmacologic activities.
- **Development stage:**
  - Solid tumors (monotherapy): Phase 1 in the U.S.

**TP-1287**  
- **Origin:** in-house (former Tolero Pharmaceuticals, Inc.), **Formulation:** oral
- TP-1287 is a small molecule oral agent that inhibits cyclin-dependent kinase 9 (CDK9). TP-1287 has shown favorable oral bioavailability in preclinical studies. It is enzymatically cleaved, yielding alvocidib, a potent inhibitor of CDK9. The oral administration of TP-1287 may allow for administration for a prolonged period, which may lead to a continuous inhibition of CDK9.
- **Development stage:**
  - Solid tumors (monotherapy): Phase 1 in the U.S.

**TP-3654**  
- **Origin:** in-house (former Tolero Pharmaceuticals, Inc.), **Formulation:** oral
- TP-3654 inhibits the inflammatory signaling pathways through inhibition of PIM (proviral integration site for Moloney murine leukemia virus) kinases. PIM kinases are frequently overexpressed in various hematologic malignancies and solid tumors, allowing cancer cells to evade apoptosis and promoting
tumor growth.

- Development stage:
  Solid tumors (monotherapy): Phase 1 in the U.S.
  Myelofibrosis (monotherapy / combination therapy): Phase 1 in the U.S.

**TP-1454**

*Origin: in-house (former Tolero Pharmaceuticals, Inc.), Formulation: oral*

- TP-1454 inhibits tumor growth through activation of PKM2 (pyruvate kinase M2) which lead to the inhibition of tumor cell proliferation and enhances antitumor immune response in tumor microenviroment. TP-1454 induces the activity of PKM2 through tetramerization of the enzyme which mainly exists in enzymatically less active dimer state in cancer cells. Tetramerization of PKM2 lead to the reduction of aerobic glycolysis in cancer cells and revert the immunosuppressive microenvironment. TP-1454 is expected to show synergistic effect with immune checkpoint inhibitor.

- Development stage:
  Solid tumors (monotherapy / combination therapy): Phase 1 in the U.S.

### 3. Regenerative medicine / cell therapy

**RVT-802**

*Origin: Duke University*

- RVT-802, a one-time regenerative therapy, is cultured human thymus tissue engineered to generate a functioning immune response when implanted in pediatric patients with congenital athymia. The key source material for RVT-802 is human thymus tissue that has been removed during pediatric cardiac surgery for unrelated conditions. Patients receive RVT-802 in the quadricep muscle during a single surgical procedure. The patient’s own bone marrow stem cells migrate to RVT-802, where they develop into mature T-cells that can fight infection. For patients who respond to RVT-802, a diverse T-cell population is established and thymic function sufficient to protect from infection usually develops between 6 and 12 months post treatment.

- Development stage: Pediatric congenital athymia: BLA submitted in the U.S. in April 2019, Complete Response Letter received in the U.S. in December 2019

### Allo iPS cell-derived products

- In cooperation with the partners in the industry-academia collaboration, we are promoting toward the commercialization of regenerative medicine / cell therapy using allo iPS cell (healthy patients) for AMD (age-related macular degeneration), Parkinson’s disease, retinitis pigmentosa, and spinal cord injury.

- Development stage:

<table>
<thead>
<tr>
<th>Development code</th>
<th>Partnering</th>
<th>Proposed indication</th>
<th>Area</th>
<th>Development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>Kyoto University CiRA</td>
<td>Parkinson’s disease</td>
<td>Japan</td>
<td>Phase 1/2 (Investigator-initiated clinical study)</td>
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<tr>
<td>HLCR011</td>
<td>RIKEN, Healis</td>
<td>Age-related macular degeneration (AMD)</td>
<td>Japan</td>
<td>Preparing for start of clinical study</td>
</tr>
</tbody>
</table>

### 4. Others

**Relugolix**

*Origin: Takeda Pharmaceutical Company Ltd, Formulation: oral*

- Relugolix is a once-daily, oral gonadotropin-releasing hormone (GnRH) receptor antagonist that reduces testicular testosterone production, the hormone primarily responsible for stimulating prostate cancer, and ovarian estradiol production, hormones known to stimulate the growth of uterine fibroids and endometriosis. Myovant has received approval in the U.S. in December 2020 for a relugolix monotherapy tablet (120 mg) for men with advanced prostate cancer. Myovant is developing a distinct product, relugolix combination tablet (relugolix 40 mg plus estradiol 1.0 mg and norethindrone acetate 0.5 mg) for uterine fibroids and endometriosis.
Profiles of Major Products under Development

- Development stage:
  Uterine fibroids: MAA submitted in Europe in March 2020, NDA submitted in the U.S. in May 2020
  Endometriosis: Phase 3 in the U.S.

**imeglimin (PXL008)**
Origin: Poxel SA, Formulation: oral
- Imeglimin has a unique mechanism of action that targets mitochondrial bioenergetics. Imeglimin acts on all three key organs which play an important role in the treatment of type 2 diabetes: the pancreas, muscles, and the liver, and it has demonstrated glucose lowering benefits by increasing insulin secretion in response to glucose, improving insulin sensitivity and suppressing gluconeogenesis.
- Development stage: Type 2 diabetes: NDA submitted in Japan in July 2020 (Co-development with Poxel)

**GEMTESA® (vibegron)**
Origin: Merck Sharp & Dohme Corp., Formulation: oral
- Vibegron is an oral, once-daily, small molecule β3 adrenergic receptor agonist. Vibegron selectively acts on the β3 adrenergic receptor in the bladder, relaxes the bladder, enhances urinary storage, and improves symptoms of urgency, urinary frequency, and urge urinary incontinence in overactive bladder. Urovant has received approval for overactive bladder in the U.S in December 2020.
- Development stage: (New indication) Overactive bladder in men with BPH: Phase 3 in the U.S.

**rodaristat ethyl**
Origin: Karos Pharmaceuticals, Inc., Formulation: oral
- Rodaristat ethyl is a prodrug of tryptophan hydroxylase (TPH) inhibitor designed to reduce peripheral production of serotonin without entering the brain. It is believed that rodaristat ethyl may halt or reverse the pathology of diseases that are driven by excessive serotonin production, such as PAH, idiopathic pulmonary fibrosis (IPF) and sarcoidosis.
- Development stage: Pulmonary arterial hypertension (PAH): Phase 2 in the U.S.

**MVT-602**
Origin: Takeda Pharmaceutical Company Ltd, Formulation: oral
- MVT-602 is an oligopeptide kisspeptin-1 receptor agonist. Activation of kisspeptin in upstream hypothalamic neurons is hypothesized to lead to the transmission of a signal that stimulates downstream neurons to increase the secretion of GnRH. Continued stimulation of kisspeptin is thought to result in the desensitization of receptor transduction, which is anticipated to result in a complete cessation of the signaling pathway. Myovant is developing MVT-602 as part of the hormonal preparation for women with infertility undergoing in vitro fertilization. MVT-602 is believed to stimulate GnRH which in turn increases secretion of luteinizing hormone that acts as a trigger for egg maturation prior to oocyte collection.
- Development stage: Female infertility: Phase 2 in Germany

**URO-902**
Origin: Ion Channel Innovations, Formulation: injection
- URO-902 is a novel gene therapy for patients with overactive bladder symptoms who have failed oral pharmacologic therapy. URO-902 is a plasmid vector containing a human cDNA encoding the pore-forming component of the Maxi-K ion channel. Expression of the Maxi-K protein in muscle cells is hypothesized to increase potassium ion flow across the cell membrane, reducing excitability of smooth muscle cells. This mechanism could potentially normalize the heightened detrusor smooth muscle tone in overactive bladder, thereby reducing the symptoms of overactive bladder.
- Development stage: Overactive bladder: Phase 2 in the U.S.
5. **Frontier business**

**SMC-01 (mobile app for management of type 2 diabetic patients) (medical device)**

- Origin: Save Medical

- The purpose of the App is to promote behavioral change in patients and improve clinical parameters by managing their daily activities related to type 2 diabetes care (meals, exercise, body weight, medication, blood pressure, and glucose level). Unlike other apps, the App is intended to be used under the guidance and endorsement of a physician, which will motivate patients to continue with their treatment and support their efforts to change their behavior.

- Development stage: Type 2 diabetes: Phase 3 in Japan (Co-development with Save Medical)