Initiatives in Drug Discovery Research

Reshape research framework, aim for further innovation

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This material contains information on pharmaceuticals (including compounds under development), but this information is not intended to make any representations or advertisements regarding the efficacy or effectiveness of these preparations, promote unapproved uses in any fashion nor provide medical advice of any kind.
Reshape Research Framework

- Reorganize Drug Discovery Research functions
- Develop Network Research System

- Integrate and intensify drug discovery and research functions
- Introduce external cutting-edge science and expand such use
- Establish Astellas Innovation Management

- Cooperate with various partners
- Expand activities of Frontier Disease Research
- Establish Regenerative Medicine Unit

- Develop new therapeutic areas and novel technology platform
- Accelerate drug discovery
- Enhance research management
- Introduce multiple R&D pathways
Restructure Organization

RPS possesses two important functions of managing research portfolio and fostering/capturing innovation. The latter is carried out in close coordination with Astellas Innovation Management.

Pharmacology Research Labs. was dissolved and restructured into TA Research Units which have enhanced autonomy and accountability.

Translational Science-related scientific and managerial capabilities are integrated to form the new TS Research Labs.

TA: Therapeutic Area
Develop New Therapeutic Areas and Novel Technology Platform
# Develop New Therapeutic Areas and Novel Technology Platform

<table>
<thead>
<tr>
<th>Activity</th>
<th>Collaboration Details</th>
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<tbody>
<tr>
<td>Apply recombinant human proteins produced by transgenic silkworms to medicine</td>
<td>• Collaboration for research with Immuno-Biological Laboratories (IBL)</td>
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<tr>
<td>Advance novel therapies for diseases and medical conditions associated with muscle weakness</td>
<td>• Collaboration for R&amp;D and commercialization with Cytokinetcs (Cytokinetcs)</td>
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<tr>
<td>Discover and develop novel drugs that improve mitochondrial functions</td>
<td>• Collaboration for R&amp;D with Mitokyne (with exclusive right to acquire the company) (Mitokyne)</td>
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<tr>
<td>Expand our commitment to regenerative medicine</td>
<td>• Establishment of Regenerative Medicine Unit</td>
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<tr>
<td>Develop RSV (Respiratory syncytial virus) vaccine</td>
<td>• Strategic partnership with ClearPath, investing in development of vaccine (ClearPath)</td>
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<tr>
<td>Discover and develop novel antibody-drug-conjugates (“ADCs”) in oncology field</td>
<td>• Collaboration for next generation ADC with Ambrx (Ambrx)</td>
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<tr>
<td>Seek more chance of innovation by diversifying compound sources</td>
<td>• Compound library sharing partnership with Daiichi Sankyo (400 thousand compounds each other) (Daiichi-Sankyo)</td>
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<tr>
<td>Collaborate with academia beyond individual corporate frameworks for discovery of novel CNS drugs</td>
<td>• Participation in LIBD consortium (LIBD)</td>
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Develop New Therapeutic Areas: Collaboration with Cytokinetics

Conduct research/development collaborations with an aim to create new innovative drugs in the field of skeletal muscle diseases.

Skeletal muscle plays a role in various organs and sites in the body. Deterioration of its functions causes various diseases and symptoms.
⇒ Aim for the development of skeletal muscle activators that will improve these symptoms.

[Progress]
- Fast skeletal muscle troponin activator CK-2127107
  - Phase I study showed dose-dependent pharmacokinetics and high tolerability
- Joint research of follow-up compounds is also progressing smoothly

Muscle structure

Target of CK-2127107

Actin (filament) and regulatory complex

Myosin

Adapted from KAMISAGO et al., New England Journal of Medicine; Volume 343 Number 23 : 1695
Develop New Therapeutic Areas: Collaboration with Mitokyne

Conduct research/development collaborations with an aim to create innovative new drugs and establish the leading position in the mitochondria-related diseases field

Mitochondrial dysfunction may cause various diseases:

- Parkinson’s disease
- Huntington’s disease
- Schizophrenia
- Alzheimer's disease
- Glaucoma
- Retinitis pigmentosa
- Dystrophia
- Sarcopenia
- Cachexia
- Sensory deafness
- Sudden deafness
- Acute kidney injury
- Chronic kidney failure
- Heart, liver, and metabolism etc.

Mitokyne Profile:
- Mitokyne has completed set up and has initiated research activities.
- Its scientific advisors include a Nobel prize laureate Dr. Horvitz.
- Nature Biotechnology selected the company as one of the Innovative startups 2013
Develop Novel Technology Platform: Initiative for Regenerative Medicine

Regenerative Medicine Unit established in April 2014

- **Mission**
  - In the field of regenerative medicine and cell therapy,
  - Generate product candidates with competitive superiority
  - Establish and maintain technology platform
  - Bear the hub function as the core research unit in Astellas

- **Organization/management structure**
  - Direct reporting to Head of Drug Discovery Research
  - Start with core research members of approximately 20
  - Plan to expand along with the progress of the research
Concept of Cell Therapy and Target of Astellas

<Expecting its multifunctionality that small compounds or biologics cannot display>

**Cell Therapy**
- Aim to recover /restore the lost function of organ or tissue by disease/aging/accident, by means of cell transplantation (administration)

**Functions of Cell**
- Structural component
- Metabolism/biosynthesis
- Sensor
- Production/release of signaling molecules

**Cell therapy Astellas targets**
- **Target indications:** Those with high unmet medical need such as cardiovascular diseases & cancer
- **Short-Mid term goal:** Recovery of function by paracrine effects of transplanted cells initiate a clinical study in a few years at the earliest.
- **Long term goal:** Recovery of function by transplanted cells themselves

**Research** using MSC, iPSC, etc
- Optimization of cell culture
- Longer storage of cells

**MSC:** Mesenchymal Stem Cell
Result of Research in Regenerative Medicine:
Research Collaboration with CiRA, Kyoto Univ. for Kidney Regeneration

CiRA: Center for iPS Cell Research and Application

Efficient generation of nephron progenitor cells from iPSC Progress for drug evaluation, disease model generation and cell therapy


Developed a method for efficient generation of nephron progenitor cells from intermediate mesoderm

In vitro 3-D culture(Left) in vivo (Right)
renal tubule specific protein was expressed and renal tubule-like structure was formed

Nephron
Nephron is the functional unit of kidney, which has glomerulus and renal tubules. There are about 1 million nephrons in a kidney.
Develop Novel Technology Platform: Strategic partnership with ClearPath for Vaccine Virosome: Membrane nanoparticle containing natural surface proteins without genetic material

- Powerful immune responses similar to a normal virus infection due to similar structure to natural RSV
- Enhancement of immune responses by the incorporation of an adjuvant
- No risk of infection due to lack of genetic material
Develop Novel Technology Platform: Ambrx Next-Generation ADC ("Antibody-Drug Conjugate")

Introduce new ADC technology with increased blood stability

**Conventional ADC**
Conjugate drug on natural amino acid residues of antibody
- Non-specific conjugation

**Ambrx ADC**
Incorporate non-natural amino acids into antibody and conjugate drug to the sites
- Site specific ADC → high efficacy
- High stability in blood → low side effects

Ambrx ADC is expected to be an anti-cancer drug with more efficacy and better safety profile

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Jackson D. et. al., PLoS One. 2014; (reported by Agensys and Ambrx)
Initiatives in Technology Platform and Focus Therapeutic Areas
Using cutting-edge Omics technologies, gain insight of diseases and actively search for drug targets/biomarkers.

Initiatives in Technology Platform: Precision Medicine/ Omics

**Analysis of Clinical sample**

- Expression proteomics: mechanism of disease
- Chemical proteomics: mechanism of drug action
- Data analysis by bioinformatics: processing information rapidly increasing

**Collaboration with Academia**

**Progress of technologies**

- New Technology (-omics, genome editing): drug target/biomarker
- Boost up Precision Medicine: Drug Discovery
Initiatives in Technology Platform: Antibody Drug Discovery and Structure Prediction

Using cutting-edge IT technologies, increase accuracy of antibody structure prediction
Promote creation of next generation antibodies

Benefits from IT revolution and Big Data

Next generation antibody drug discovery

Development of antibody informatics

3D modeling  dynamic simulation

Antibody Sequence

(1D information)

Prediction

(3D information)

Prediction

(4D information)

IBC’s 24th Antibody Engineering and Therapeutics

International competition of antibody structure prediction
(The second competition in December 2013)

- A team of Osaka University, National Institute of Biomedical Innovation, and Astellas predicted most correctly.
Achievement in Oncology Research:
ASP2215 (Novel FLT3/AXL Inhibitor)

ASP2215, a FLT3/AXL inhibitor, showed potent antileukemic activity against AML with either or both FLT3-ITD and FLT3-D835 mutations.

Mori et al., 2014 ASCO Annual Meeting

Kinase inhibitory profile

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<tr>
<th>Kinase</th>
<th>IC$_{50}$ (nmol/L)</th>
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<tbody>
<tr>
<td>FLT3</td>
<td>0.29</td>
</tr>
<tr>
<td>LTK</td>
<td>0.25</td>
</tr>
<tr>
<td>ALK</td>
<td>0.42</td>
</tr>
<tr>
<td>AXL</td>
<td>0.70</td>
</tr>
<tr>
<td>TRKA</td>
<td>1.1</td>
</tr>
<tr>
<td>RET</td>
<td>1.8</td>
</tr>
<tr>
<td>ROS</td>
<td>1.5</td>
</tr>
<tr>
<td>MER</td>
<td>2.9</td>
</tr>
<tr>
<td>c-KIT</td>
<td>230</td>
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</table>

ASP2215 is a potent FLT3/AXL inhibitor.

Antitumor activity of ASP2215 in mice xenografted with MV4-11 cells

ASP2215 induced complete remission in mice FLT3-ITD xenograft model at doses of 6 mg/kg and above.
Binding Affinity (KINOMEscan®)

<table>
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<tr>
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<th>Kd (nM)</th>
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<tr>
<td>wild type</td>
<td>140</td>
</tr>
<tr>
<td>T790M/L858R</td>
<td>0.22</td>
</tr>
</tbody>
</table>

ASP8273 showed higher affinity to EGFR T790M/L858R than wild type EGFR.

ASP8273 induced tumor regression in NSCLC xenograft model with EGFR T790M/L858R at doses of 10 mg/kg and above.

Sakagami et al., AACR Annual Meeting 2014
Summary

Reshape research framework, aim for further innovation

- More utilizing external resources with Network Research System
- Develop new therapeutic areas and novel technology platform
- Continue enhancing current technology platform and focus therapeutic areas