Science-based Initiatives of PMDA

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Today’s Presentation

1. Introduction: Products from Japan
2. Current Status of Pharmaceutical Affairs Consultation on R&D Strategy
3. Updates of Science Board
4. Advanced Review/Consultation System
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EML4-ALK fusion oncogene

Professor Hiroyuki Mano (Jichi Medical University, Japan) discovered EML4-ALK fusion oncogene in non-small-cell-lung cancer in 2007.

(Nature 2007; 448:561-6)

Crizotinib
Alectinib
PD-1 (programmed cell death 1)

Professor Tasuku Honjo (Kyoto University, Japan) identified PD-1 in 1992 (EMBO J. 1992 Nov;11(11):3887-95.).

Anti PD-1 Antibodies
CCR4: Molecular target of Adult T-cell leukemia (ATL)

Professor Ryuzo Ueda (Nagoya City University, Japan) discovered CCR4 as the pathogenic factor of ATL (Clinical Cancer Res 2003; Sep 1; 9(10 Pt 1):3625-34)

Mogamulizumab : Anti CCR4 mAb
(POTELIGEO® Injection, Kyowa-Kirin Co., Ltd.)

Approved in JAPAN; March 2012 for ATL (First marketing authorization)

POTELIGEO® (Mogamulizumab) is a humanized monoclonal antibody targeting CCR4 developed by Kyowa-kirin Co., Ltd. It is considered to bind with CCR4, suppressing tumor growth by antibody-dependent cellular cytotoxicity (ADCC).
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Pharmaceutical Affairs Consultation on R&D Strategy

Valley of Death between Basic research & Practical Use
- Shortage of funds, Knowledge on Regulation and developmental strategy

Consultation on pre-clinical requirements
- quality, efficacy, and safety
- tumorigenicity,
- biological ingredient safety

Consultation on early clinical trial
- Endpoints
- sample size of early clinical trial
  (Up to POC studies)

Flow of Strategy Consultation
  Introductory Consultation (775)
  Pre-Consultation (937)
  Face-to-Face Consultation (236)

(7/1/2011 – 10/31/2014)
## Case of Face to Face consultation

<table>
<thead>
<tr>
<th>Consulter</th>
<th>Product under development</th>
<th>Intended performance, Intended use, Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Institute of Neuroscience, NCNP Department of Molecular Therapy, Shin’ich Takeda</td>
<td>Morpholino oligos (Antisense)</td>
<td>Remedy for Duchenne muscular dystrophy (DMD)</td>
</tr>
<tr>
<td>Molecular Medicine and Therapy, Medicine (ART), Tohoku University School of Medicine, Toshio Miyata</td>
<td>PAI-1 Inhibitor (TM5509)</td>
<td>Hematogenic recovery of cord blood transplantation</td>
</tr>
<tr>
<td>Center for iPS Cell Research and Application (CiRA), Kyoto University, Shinya Yamanaka</td>
<td>iPS Cell (Allo)</td>
<td>Starting Materials for cellular &amp; tissue based products derived from iPS Cells</td>
</tr>
<tr>
<td>Sapporo Medical University, Osamu Honmou</td>
<td>Mesenchymal Stem Cell (Auto)</td>
<td>Improvement of neurological sign, activities of daily living disorders in daily activities, and dysfunction associated with Stroke</td>
</tr>
<tr>
<td>CYBERDYNE INC.</td>
<td>ROBOT SUIT HAL (Hybrid Assistive Limb®) and partial Equipment for the subset of function of HAL used for movement training</td>
<td>Devices for assistive movement with in patients. Planed to introduce models which differ in intended use or indications.</td>
</tr>
</tbody>
</table>
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### Establishment of the Science Board

The Science Board was established in May 2012 to discuss how PMDA can better cope with products with advanced science & technology, in each developmental stage such as basic research, development support, product review, and post market safety measures.

### Board members

- **Academia**
- **Board members**
- **Office of Review Innovation**

### Office of Review Innovation

- **Basic Research**
  - Seeds of new drug / medical devices
  - Quality Tests
  - Non-clinical tests
  - Clinical Trial Consultation
  - Review
  - Approve
  - Post Marketing Safety Measure

### Practical use

- **Innovative medical products**
  - Office of Review (Drugs & Medical Devices), Office of Safety

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**Flowchart:**

1. **Basic Research**
2. **Quality Tests**
   - Non-clinical tests
3. **Clinical Trial**
4. **Review**
5. **Approve**
6. **Post Marketing**

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**Pharmaceutical consultation on R&D Strategy**

**Clinical Trial Consultation**

**Review**

**Post Marketing Safety Measure**

**Seeds of new drug / medical devices**

**Practical use**

**Innovative medical products**

**Establishment of the Science Board**

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**Office of Review Innovation**

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**DIA DEVELOP INNOVATE ADVANCE**

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**12**

**Pharmaceuticals**
Recommendation for the review policy of the pharmaceuticals regarding personalized medicine and discussion of needed items in order of priority.

**Cellular & Tissue-based Products**
How to ensure the safety of cellular and tissue-based products and aiming at revealing the predictable risks in the products as possible.

**Medical Devices**
Starting from discussion about the common issues as many kind of medical devices as possible because of big differences among product attributes of the medical devices.
Outcomes of the Science Board
(1st Stage: Jul. 2012-Mar. 2014)

Cellular & Tissue-based Products
- Current Perspective on Evaluation of Tumorigenicity of Cellular and Tissue-based Products Derived from iPSCs and iPSCs as Their Starting Materials (Aug. 21, 2013)

Pharmaceuticals, Bio-based Products
- Summary of Discussion on Non-clinical Pharmacology Studies of Anticancer Drugs (Dec. 10, 2013)
- Summary of the discussion on assessment of the current status of personalized medicine related to development and review (Mar. 11, 2014)
Current Perspective on Evaluation of Tumorigenicity of Cellular and Tissue-based Products Derived from induced Pluripotent Stem Cells (iPSCs)* and iPSCs as Their Starting Materials

Tatsutoshi Nakahata, Chair, Cellular and Tissue-based Products Subcommittee
Hideyuki Okano, Vice-chair, Cellular and Tissue-based Products Subcommittee

1. Introduction
The Cellular and Tissue-based Products Subcommittee (hereinafter, the subcommittee) of the Science Board to Pharmaceuticals and Medical Devices Agency (PMDA) has held multiple discussions from the scientific point of view on “tumorigenicity” that is the major safety concern of induced pluripotent stem cells (iPSCs)* for cellular and tissue-based products, and come to conclusion at present of

*IPS 細胞等を

 Provisional Translation (as of September 30, 2013)†

August 20, 2013
Subcommittees on 2nd Stage (Apr 2014- Mar 2016) and Their Activities (till Feb 2014)

Drug Area
1. Subcommittee on Placebo-controlled Trials (held twice)
2. Subcommittee on Non-clinical Studies (held 3 times)

Medical Device Area
3. Subcommittee on Application of Numerical Analysis to Non-clinical Evaluation (held 3 times)
4. Subcommittee on Evaluation of Medical Devices for Pediatric Use (held twice)

Cellular & Tissue-based Products Area
5. Subcommittee on Cell Processing Center (held 4 times)
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Advanced Review/Consultation System

Analysis by PMDA
- Giving additional scientific value to submitted data

Cooperation with Academia

Regulatory Science

Practical use of Innovative Medical Products
- A rational & effective evaluation process for regulatory decision

Effective and High Quality Review
- More predictable efficacy/safety after approval
- Reduction of applicant’s work load
- More scientific regulatory decision

Effective and Successful Development
- Epoch-making proposal leading the world
- Proactive publication of guideline

Cross-Products Analysis
- Innovative evaluation methods
- Active utilization of Modeling & Simulation
  - Disease model
  - Objective B/R assessment
  - Identifying AE-related factors etc.

Sophisticated NDA review
- Each reviewer utilizes innovative assessment techniques

Sophisticated Consultation
- More evidence-based consultation
Utilization of study data and expected outcomes

<table>
<thead>
<tr>
<th>Subject</th>
<th>Outcome</th>
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<tr>
<td>Prediction of drug interaction using a model</td>
<td>• Increase of study success rate</td>
</tr>
<tr>
<td>Development of a dose-response model and prediction of optimal dose</td>
<td>• Avoidance of unnecessary studies</td>
</tr>
<tr>
<td>Development of a new evaluation indicator for disorders with no</td>
<td>• Confirmation of model</td>
</tr>
<tr>
<td>appropriate indicator</td>
<td>• Appropriateness in the review process</td>
</tr>
<tr>
<td>Identification of factors affecting efficacy or safety</td>
<td>• Decrease of regulatory inquiries</td>
</tr>
<tr>
<td>Evaluation of class effect in rare adverse events</td>
<td>• Enhanced safety prediction, etc.</td>
</tr>
<tr>
<td>Prediction of QT prolongation based on simulated blood concentration-QT</td>
<td></td>
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Others: Evaluation of clinical data from Japanese subjects, comparison with those from non-Japanese subjects, etc.
Task Force for Advanced Review / Consultation

Established on Sep. 1st, 2013

Senior Executive Director

Steering Committee
Relevant board members/executives

Support team
Relevant directors and persons in charge

Advanced Review with Electronic Data Promotion Group

Administrative office
IT group
Business group

Opinion exchange

Regular opinion exchange meeting on new drug

Review WG
WG for constructing the framework for utilizing electronic study data

FY 2016: Submission of electronic clinical data for MAA
After FY 2017: Submission of electronic non-clinical data for MAA
Summary

- *Pharmaceutical Affairs Consultation on R&D Strategy* is offering consultation for innovative products developed by academia/venture businesses.

- *Science board* was established for review/consultation in PMDA to become more science based.

- PMDA is going to develop a *next generation reviewing system* by accumulating electronic data.
Thank You for attention!

Dr. Takao Yamori
Director of Center for Product Evaluation, Pharmaceuticals and Medical Devices Agency (PMDA)

http://www.pmda.go.jp/