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Novel Regulatory Science Research on Drugs for Alzheimer's Disease

-A Guideline on the Clinical Evaluation of Drugs for Alzheimer's Disease (Interim Report)-

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Disclosure of conflict of interest

There are no companies, etc. in a relation of conflict of interest requiring disclosure in relation to the presentation.

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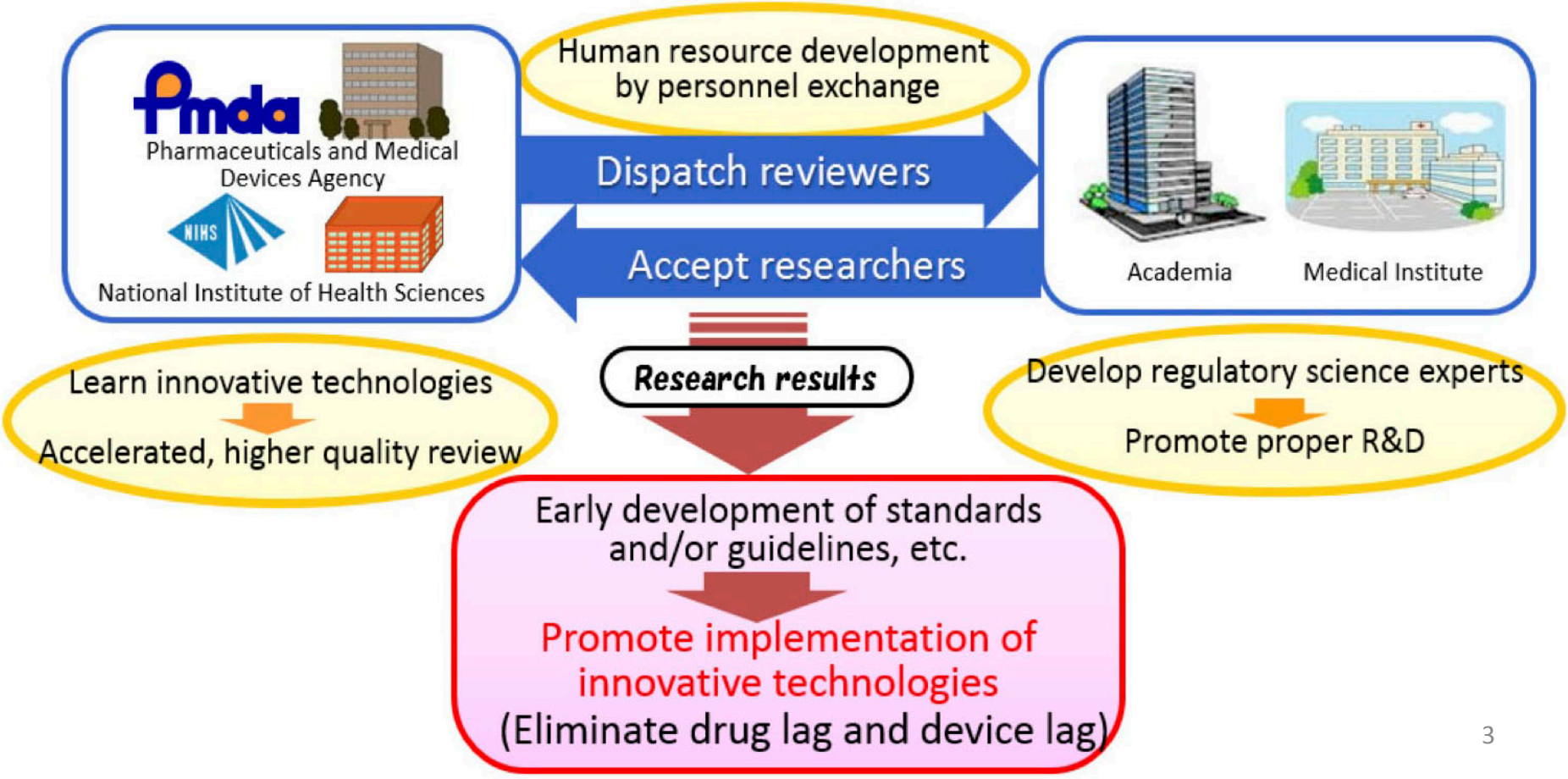
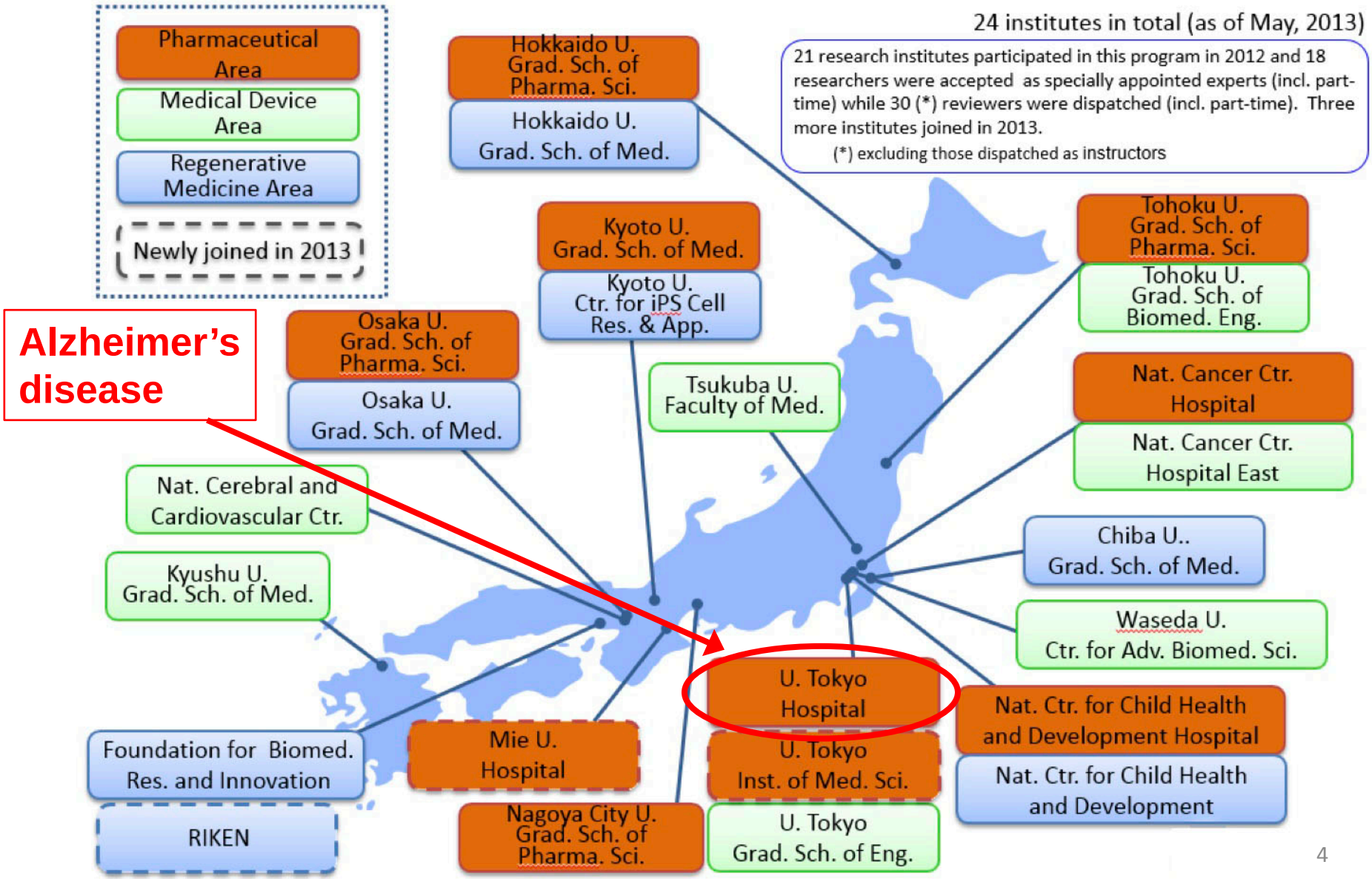
Regulatory Science Research Project in Japan

MHLW launched a project termed "Accelerating regulatory science initiatives" to promote the development of innovative drugs and its approval review in 2012.



Academic Institutions Involving in the Project



Regulatory science research on the drug development for Alzheimer's disease

【Objective】

Establish standards for clinical evaluation of drugs for Alzheimer's disease (AD)

【Methods】

- **Simulations and analyses on histories obtained from ADNI and clinical trials**

【Goals】

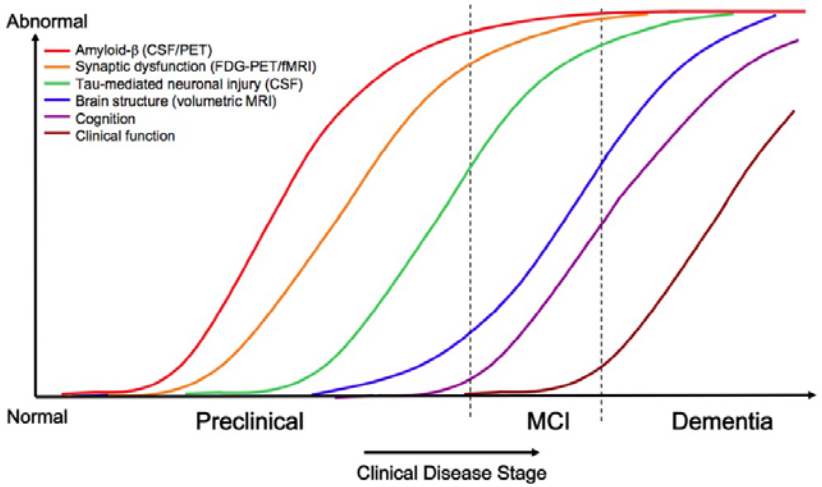
- **Facilitate development of new anti-AD drugs**
- **Facilitate establishment of standards for evaluation of new anti-AD drugs**

(1) Establishment of Standards for Clinical Evaluation of Anti-AD Drugs using Biomarkers

AD Neuroimaging Initiative

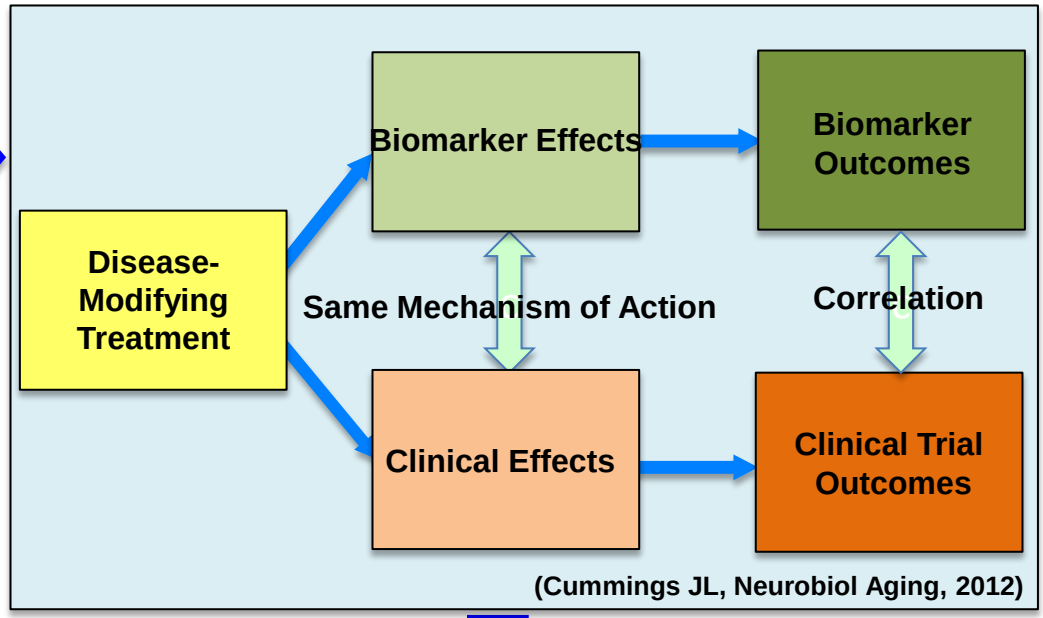
Neuroimaging（PET・MRI）
Biomarker (peptide levels)
Cognitive function test

Clinical trials, simulations, and etc.



(Sperling RA, et al., Alzheimers Demnt, 2011)

NIA/AA (2011)	Preclinical AD	MCI due to AD	AD dementia
Dubois (2010)	AD pathology	Prodromal AD	AD dementia



(Cummings JL, Neurobiol Aging, 2012)

Establish standards (guideline) for evaluation of new anti-AD drugs

Support development of innovative drugs

(2) Extension of M & S for prediction of therapeutic benefit of anti-AD drugs

AD Neuroimaging Initiative
Neuroimaging (PET・MRI)
Biomarkers (peptide levels)
Cognitive function test

→ Developmental process of AD from appearance of amyloid β, then neuronal injury, volumetric change of brain, and finally to dementia

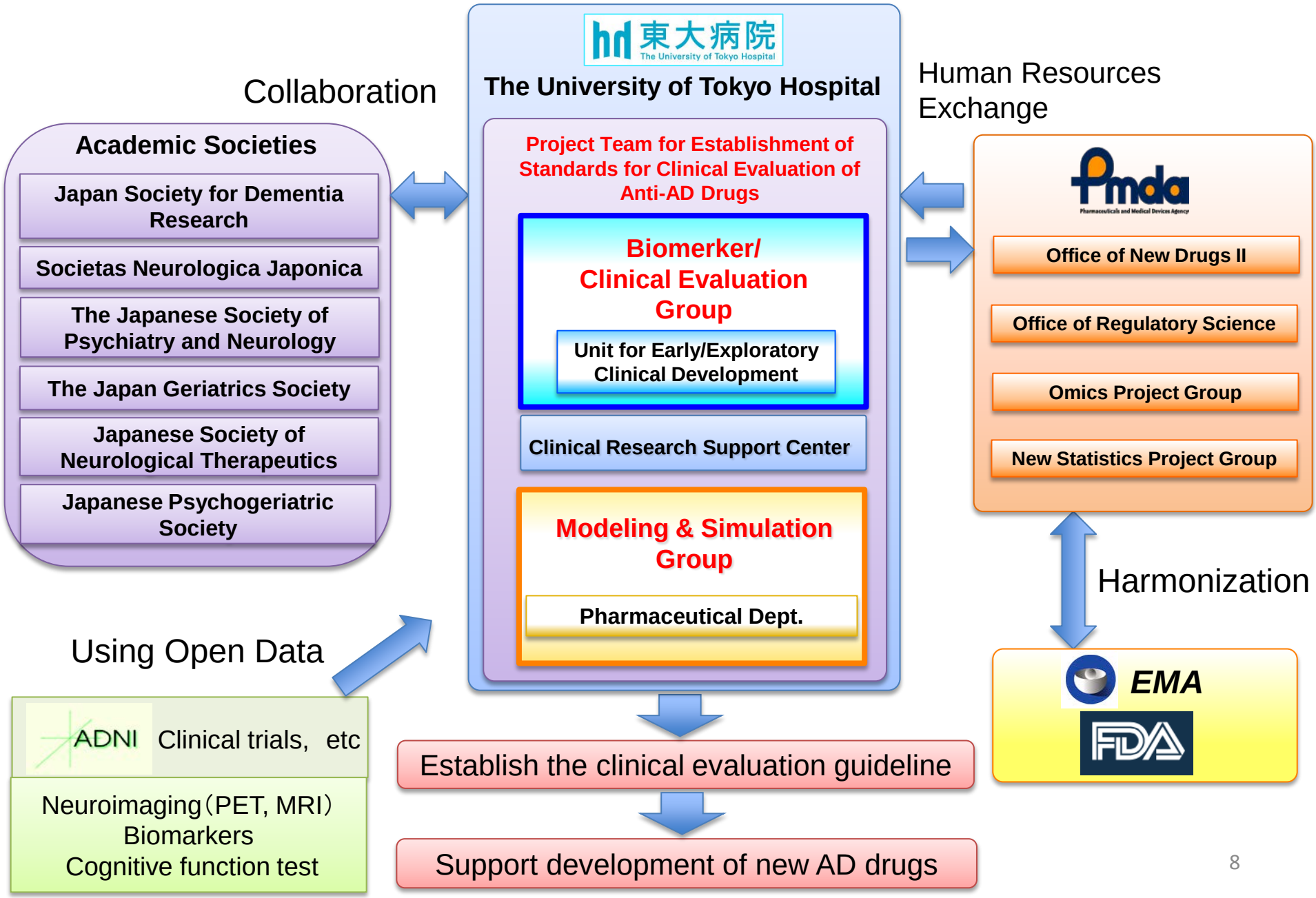
Extension of Modeling & Simulation (M&S)

Disease model	Drug model	Trial model
Biology	**Pharmacology**	**Pharmacometrics**
Natural progression	Mechanism of action	Patient population
Biomarker(s) / Imaging	Effectiveness	Method validation
Genetic effect(s)	Safety	Statistic significance

(Gobburu JV, et al., Annu Rev Pharmacol, 2009)

① M & S technique developed by this project will be applied to the POC clinical trials of the new anti-AD drug currently being developed by the University of Tokyo.
② Robustness of the model will be improved by applying outcomes of various clinical trials including overseas.

Structure


Collaboration
Academic Societies
Japan Society for Dementia Research
Societas Neurologica Japonica
The Japanese Society of Psychiatry and Neurology
The Japan Geriatrics Society
Japanese Society of Neurological Therapeutics
Japanese Psychogeriatric Society
東大病院 The University of Tokyo Hospital
The University of Tokyo Hospital
Project Team for Establishment of Standards for Clinical Evaluation of Anti-AD Drugs
Biomerker/ Clinical Evaluation Group
Unit for Early/Exploratory Clinical Development
Clinical Research Support Center
Modeling & Simulation Group
Pharmaceutical Dept.
Human Resources Exchange
Pmda
Office of New Drugs II
Office of Regulatory Science
Omics Project Group
New Statistics Project Group
Harmonization
EMA
FDA
Using Open Data
ADNI Clinical trials, etc
Neuroimaging（PET, MRI）
Biomarkers
Cognitive function test
Establish the clinical evaluation guideline
Support development of new AD drugs

Expected Outcome

- **Propose reasonable standards for clinical evaluation of new anti-AD drugs worldwide**

- **Establish Japanese guideline and facilitate development of anti-AD drugs**

Guideline Development for Drugs for Alzheimer's disease

- “Issues to Consider in the Clinical Evaluation and Development of Drugs for Alzheimer’s Disease” (Interim Report)
- “Interim Report” was released to the public in November 2013.
- Many comments have been submitted from industry and academia in Japan.

Outline

- Inclusion Criteria
- Efficacy Endpoint
- Clinical Development in Japan
- Preclinical AD

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Inclusion Criteria

- We recommend to use biomarkers
  - To exclude patients who don't have AD pathology.
  - (In case of pre-dementia stage) To administer drugs only to patients who have higher risk of developing dementia.

Inclusion Criteria

- However, further validation and standardization are needed.
  - Measurement variability
  - Differences between Japanese and non-Japanese are unclear (e.g. cut-off value).
  - Further investigations in Japanese population are needed.
    - J-ADNI
    - Biomarker information in clinical trials

Measurement of Biomarkers in Post-Marketing Clinical Practice

- Basically, the biomarkers used to select subjects in clinical trials should be available in clinical practice in the same way.

- Description in drug labeling about the necessity of measuring biomarkers before administering the drug would be determined based on the risk/benefit of the drug and the medical practices at the time of NDA.

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Efficacy Endpoint

- AD dementia
  - Co-primary endpoints are required.
    - Cognition
    - Activities of daily living
      or
      Global assessment

Efficacy Endpoint

- Pre-dementia stage of AD
  （e.g. MCI due to AD)
  - Time to a diagnosis of dementia
    - Sufficient training for clinical investigators is necessary to reduce variability.
  - Composite scale of cognition and function
    - Clinical meaningfulness must to be explained.
    - Efficacy of the drug should be supported by the result of the secondary endpoint.

      (e.g. separate scales, time to event)

Use of Biomarkers as Efficacy Endpoint

- The relationship between biomarkers and clinical effects induced by drug intervention has not been fully understood yet.
- At present, it is recommended to evaluate biomarkers as secondary endpoint.
- Information of biomarkers is also important to obtain disease modifying claim.

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Clinical Development in Japan
- Phase I Study -

- Most of drugs for Alzheimer's disease have been developed by global clinical trials.

- Basically, Phase I study to investigate safety and pharmacokinetics is required in Japanese population.
  - Investigation of ethnic differences
  - Biomarker information

Clinical Development in Japan
- Phase II Study -

- Phase II study to explore dose-response relationship in Japanese population is required in principle.
  - Participate in global phase II study
  - Conduct domestic phase II study before global Phase III study
- Basically, dose-response relationship should be investigated on the basis of the clinical symptoms not on biomarkers, at present.

Clinical Development in Japan
- Phase II Study -

- Pre-dementia stages of Alzheimer's disease
  - Need to consider the feasibility to conduct clinical trials in Japan.
  - If dose-response relationships could be investigated and robust efficacy could be demonstrated within one large scale and long-term clinical trial (e.g. seamless phase II/III study), conducting another phase III study may not be required.

Clinical Development in Japan
- Phase III Study -

- Global phase III study should have a design, in which consistency of the result in primary endpoint can be obtained between Japanese population and entire population.
- The method for calculating sample size of Japanese population to obtain the consistency is described in the notification.

http://www.pmda.go.jp/kijunsakusei/file/guideline/new_drug/GlobalClinicalTrials_en.pdf

Outline

- Inclusion Criteria
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- Preclinical AD

Preclinical AD

- Further discussion is needed
  - Approval System
  - Feasibility to conduct long-term placebo control study as post-approval study

- J-ADNI2 project, which investigate natural course of preclinical AD, has been just started.

Conclusion

- Using Biomarkers is recommended
  - Patient selection
  - Secondary endpoint
- Further validation is needed
  - Especially in Japanese population
- Increasing global clinical trial
  - Participating in global study from early stage of development is recommended
- We would like to continue the discussion with industry, academia and other regulatory authorities.

Thank you for your attention!