Industry Perspective World-Wide ADNI

North American-ADNI Private Partner Scientific Board (PPSB)

World-Wide ADNI Meeting
Vancouver, Canada, July 13, 2012

Johan Luthman, PPSB Chair 2012 (Merck & Co Employee)

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Benefits of ADNI PPSB Partnership

Membership in the ADNI PPSB provides partners with opportunities to:

- Participate in an independent, pre-competitive forum for study-related scientific exchange among partners
- Participate in open ADNI Core discussions
  - Biomarkers, Biostatistics, Clinical, Genetics, MRI, Neuropathology, PET and Publications
- Engage and contribute to Biomarker progression via dedicated PPSB Working Group efforts
- Interact with ADNI PI/Core Leaders, colleagues from Pharma & Diagnostics companies, NIH and Regulators
- Network to other AD initiatives/organizations, such as Alzheimer's Association, Critical Path Institute (CAMD)
- Opportunities to engage in WW-ADNI network

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Impact of PPSB

- Partnership structure is the “gold standard” for an effective public-private partnership.

- Captive audience & provide input to other initiatives
  - For example National Alzheimer’s Project Act sponsored fora (e.g., Alzheimer’s Disease Research Summit 2012)

Current PPSB Partners in NA-ADNI

- Private partners committed more than $45 million to AD research through NA-ADNI (ADNI1 and ADNI2)
- Major contributions from industry also to J-ADNI, Pharma-Cog, etc.
  - ➢ However, challenges for industry to participate across WW-ADNI initiatives

Meso Scale Diagnostics, LLC.

NOVARTIS

Pfizer

Roche

SERVIER

SYNARC
Start here, finish first.

Takeda

Canadian Institutes of Health Research

Instituts de recherche en santé du Canada

alzheimer's association

Alzheimer's Drug Discovery Foundation

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Industrial Aspect on WW-ADNI

Key Deliverables from ADNI to Rx & Dx Industry:

Redefinition of Disease Stages

- Identification of pre-dementia AD in MCI populations
- Feasibility Prodromal AD trials (pivotal drug trials)

New Diagnostics & Prognostic Tools

- Biomarker discovery & feasibility
- Biomarker supported diagnosis (diagnostic markers)
- Biomarker supported trial read-out (prognostic markers)

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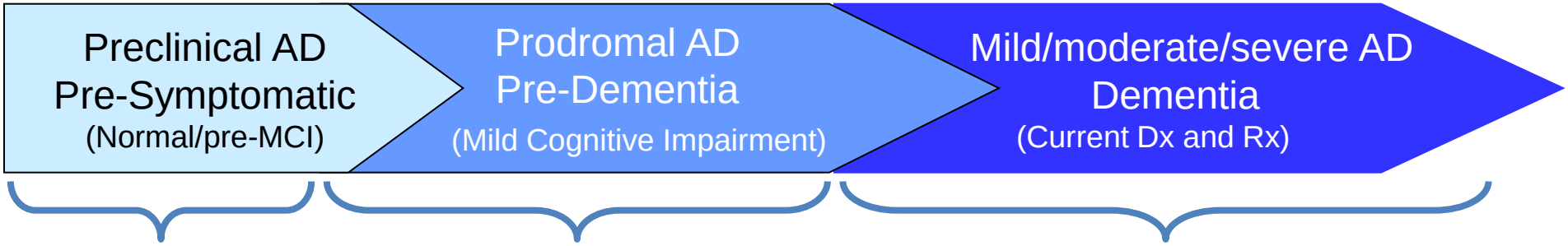
Redefinition of Disease Stages



Subjects with risk factors; family history, dominant mutations or ApoE4 genotype **Early intervention may stop disease to occur**	**Pre-dementia form of AD identified by mild cognitive complaints and positive biomarker profiles** **Early intervention may stop progression to AD diagnosis**	**Current AD diagnosis based on clinical symptoms; dementia of the Alzheimer's disease type** **Symptomatic treatment with AChEI or memantine**
Primary/secondary prevention	**Prevention of dementia**	**Treatment of Dementia**

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Redefinition of Disease Stages

Prodromal AD

- Alzheimer's Disease Neuro-Imaging Initiative: ADNI-1 / ADNI GO / ADNI-2)
  - Late – MCI, Early - MCI
- World Wide "ADNI" efforts: PharmaCog (IMI/EU), AIBL (Australia), Japan-ADNI, etc.

➢ **Major impact on biomarker supported diagnosis of AD and definition Prodromal AD**

Pre-symptomatic AD

- Alzheimer's Prevention Initiative (API)
  - PSEN1 carriers (Colombia) + APOE4 carrier populations (US)
- Dominantly Inherited Alzheimer's Network (DIAN)
  - Preventative trials in autosomal dominant subjects (USA + EU)
- US Department of Defense – TBI veterans
- Several other initiatives on biomarker changes in Pre-symptomatic AD

➢ **Critical need to move further "upstream" in disease process to build feasibility for prevention trials**

Strategic Intent with AD biomarkers

Early Development–biomarker for target engagement & proof of principle

- **"Fit for purpose" biomarker in Phase I and II clinical trials**

Late Development – Prognostic Biomarkers to support drug label claims

- **Treatment outcome measure (prognostic) in pivotal trials**
- **Support of efficacy claims on disease modification effects**

"Independent" Stand alone Diagnostic (vMRI, PET Imaging, IVD etc.)

- **Not associated with specific drug**

Companion Diagnostic - Pharmacodiagnostic (IVD with Drug)

- **Post-drug development – Developed after drug launch; label update**
- **Pre-drug development – Already commercialized test used in drug trial**
- **Co-development– "True" CoDx with co-approval of Rx and Dx**

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Application & Maturity of AD Biomarkers

Technology	Application			Stage of maturity
Amyloid PET Imaging **Binary read** **SUVR**		Diagnostic +++	Prognostic ?	• **Regulatory approved technology** • **Reader standardization** • **Late stage clinical qualification** • **Use in Ph II trials**
volumetric MRI **- Hippocampal volume** **+ Ventricular size**		Diagnostic +	Prognostic +++	• **Used in trials as secondary read out** • **Standardization** • **Commercialization**
CSF signature **- Aβ42; + Tau, P-Tau** **+ Tau/Ab42 ratio**		Diagnostic +++	Prognostic (Tau) ?	• **Assay standardization** • **Late stage clinical qualification** • **Use in Ph II trials**
FDG PET Imaging **Binary read** **SUVR**		Diagnostic (+)	Prognostic ++	• **Standardization** • **Clinical qualification remains**
Genotyping **ApoE genotype** **FAD: APP, PSEN ½** **Other risk genes**	Antecedent +++	Diagnostic (ApoE) +		• **Common tests** • **Standard in trials**
Blood biomarkers **Protein signatures** **mRNA signatures**		Diagnostic ?		• **Analyte identification ongoing** • **Early stage clinical qualification**
Tau PET Imaging		Diagnostic ?	Prognostic ?	• **Moving into Phase I evaluation**

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Amyloid PET Imaging Binary read SUVR	ostic	Pr… c ?	• Regulatory approved technology • Reader standardization • Late stage clinical qualification • Use in Ph II trials
volumetric MRI - Hippocampal volume + Ventricular size			• Used in trials as secondary read out • Standardization • Commercialization
CSF signature - Aβ42; + Tau, P-Tau + Tau/Ab42 ratio			• Assay standardization • Late stage clinical qualification • Use in Ph II trials
FDG PET Imaging Binary read SUVR			•Standardization •Clinical qualification remains
Genotyping ApoE genotype FAD: APP, PSEN ½ Other risk genes			•Common tests •Standard in trials
Blood biomarkers Protein signatures mRNA signatures			•Analyte identification ongoing •Early stage clinical qualification
Tau PET Imaging	ostic	Pr… c ?	•Moving into Phase I evaluation

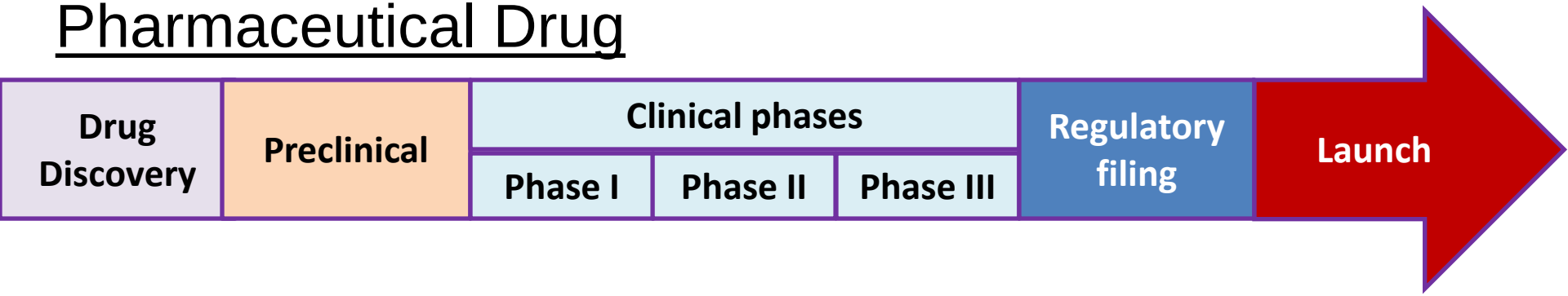
New trial populations

New trial read-outs

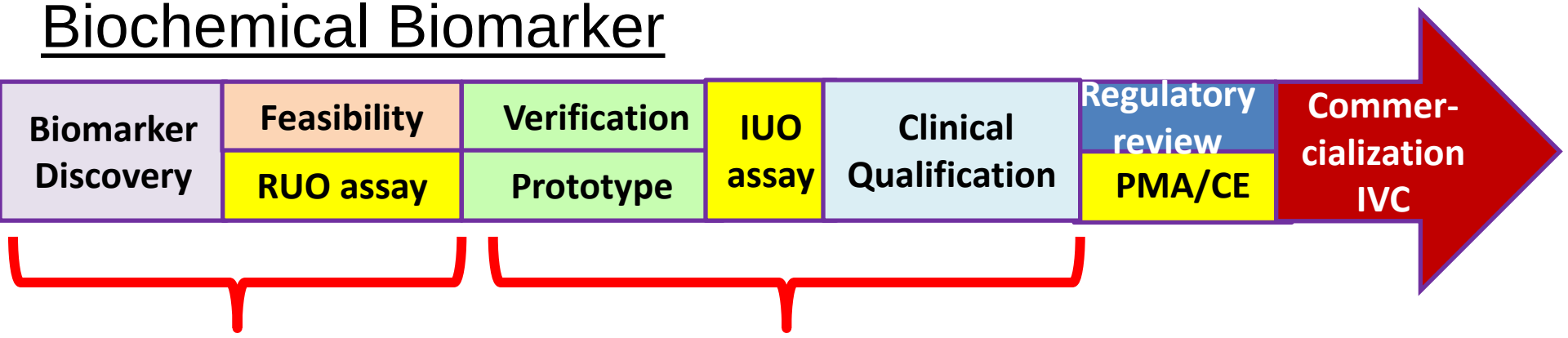
National Institutes of Health

Companion Diagnostic Pathway

Pharmaceutical Drug



Biochemical Biomarker



ADNI Effort

- **Individual Dx/Rx companies**
- **Other Private-Public Partnerships**

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Efforts of Recently Formed PPSB-Initiated Working Group

- Biofluid Biomarkers Working Group
  - Collaborating on efforts to identify blood-based and CSF biomarkers for prodromal AD phase III trials – Forum for Dx and Rx companies to meet in general technical and scientific discussions
  - Supplementary effort to the Alzheimer's Association Global Biomarkers Standardization Consortium's Initiatives, CAMD, etc.

Standardization of CSF biomarker assays

- Global Consortium for the Standardization of Biomarkers (Alz. Assoc.)
  - Reference Material & Methods effort for CSF Biomarkers
  - Collection, storage and sample processing
- ADNI - PPSB: Biomarkers Working Group
  - Align efforts on CSF IVD between Pharma and Diagnostics Companies

Regulatory interactions biomarker qualification

- Critical Path Institute/CAMD:
  - Qualification opinions requests: vMRI (EMA & FDA), CSF BMx (FDA) etc.
- Individual Pharmaceutical or Diagnostic companies:
  - Qualification opinions requests: CSF BMx (EMA) and Amyloid PET (EMA)

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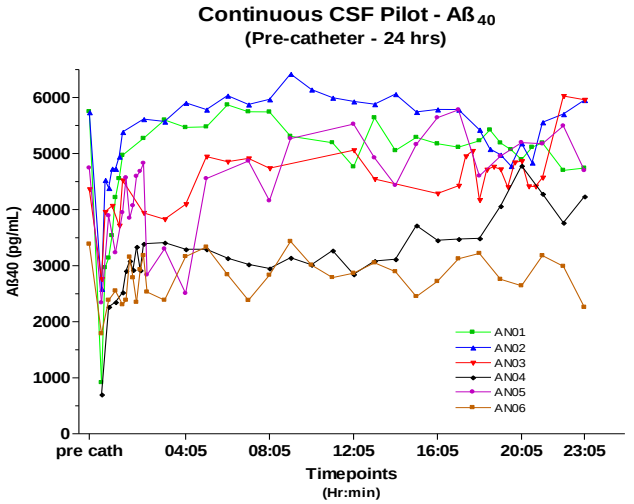
Past Efforts
PPSB Working Groups/ fNIH Consortium

- Plasma Proteomics project
  - fNIH Biomarkers Consortium (special support Pfizer)
  - ADNI-I plasma samples - RMB analyses; Data delivered 2010
- A Beta as a Biomarker Working Group
  - CSF Placebo “drift” precompetitive study (PPSB only)
  - Healthy volunteer placebo phase I studies with continuous CSF sampling (and monkey data)
  - Analyze possible causes of the “drift” issue

- **Biological reason?**
  - CSF flow effect
  - Subject dependent
  - Leakage differences
- **Technical reason?**
  - Stickiness to the catheter
  - Aggregation of the peptide



Ongoing Efforts via fNIH Consortium

- CSF Targeted Proteomics Project
  - fNIH Biomarkers Consortium
  - ADNI-I CSF samples
  - RMB analyses
  - Abstracts/posters at AAIC meeting in Vancouver

  - BACE1 activity (and sAPPbeta)
    - Merck sub-study
    - Data subnitted to ADNI April, 2012

Current Efforts of Established PPSB-Initiated Working Groups

- Informatics Working Group (formerly Database Working Group)
  - Working with Core Leader(s) to improve ADNI data interrogation systems
- PET Imaging Endpoints Working Group
  - Collaborating with existing initiatives to identify early AD imaging biomarkers and standardize Amyloid PET tracers
- Neuropsychology & ADAS-Cog PLUS Working Groups
  - Identify and/or develop clinical rating instrument for prodromal AD based on ADAS-Cog data set from ADNI-I
  - Supported by subgroup of NA-ADNI PPSB companies

New Initiative
PPSB-Initiated Working Group

- Clinical End Points Working Group
  - To provide a forum for dedicated research and analyses by PPSB members to further unlock the potential of ADNI cognitive and functional data for future clinical trial design
    - An improved understanding of cognitive and functional trajectories in specific populations on existing endpoints
    - A critical appraisal of methodologies and development of an acceptable “toolbox” for endpoint optimization and novel endpoint development
    - New endpoints derived from data on existing measures with improved performance in specific populations

PPSB Perspective of WW-ADNI

- Data from global sites provide biochemical biomarker (CSF and plasma), MRI, and PET data on various populations (ethnic etc.) for use in planning phase III trials
  - Highlight global standardization challenges (e.g. CSF measures differences)
- Understanding the global technical and logistical challenges with biomarker supported patient recruitment
  - Differences in SoC, use of biomarkers, infra-structure
- Opportunities to learn from different regulatory agencies (e.g. FDA, EMA, PMDA, etc.)

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2012: An Exciting Year for Alzheimer's Disease

- Proof of Concept for anti-Aβ monoclonal antibodies (Aβ clearance principle)
- β-secretase inhibition moves into patients (Aβ reduction principle)
- Gamma-secretase inhibition further clarified
- Regulatory approval of an Amyloid PET ligand
- Critical progression of AD biomarker qualification efforts
- Initiatives of National Alzheimer's Project Act

And much more this year……..

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