Proposal for Launching K-ADNI

(Korean Alzheimer's Disease Neuroimaging Initiative)

December, 2010

K-ADNI Launching TFT

1. **Goals**

    1. To establish Korean ADNI that complies with international standards of world-wide ADNI for development of new drugs for Alzheimer's Disease dementia patients.

    2. To evaluate the effects of vascular risk factors on; (1) Alzheimer's disease progression, (2) Subcortical Vascular Dementia (SVaD) which comprises relatively large proportion of Asian dementia patients.

    3. To establish the efficacy approval system for new dementia drugs.

2. **Background**

    1. **Diagnosis for dementia and monitoring its progression is very difficult.**

        1. Disease onset and progression is very slow to be detected reliably.

        2. Cognitive decline due to ageing process or to dementia is difficult to discern.

        3. MRI scan of the brain cannot reliably differentiate ageing related volume loss and pathological changes.

        4. Amyloid protein deposition in the brain can be detected by PET imaging, but we are still not sure if this material is the culprit.

        5. The usefulness of laboratory tests on blood or CSF samples are very limited.
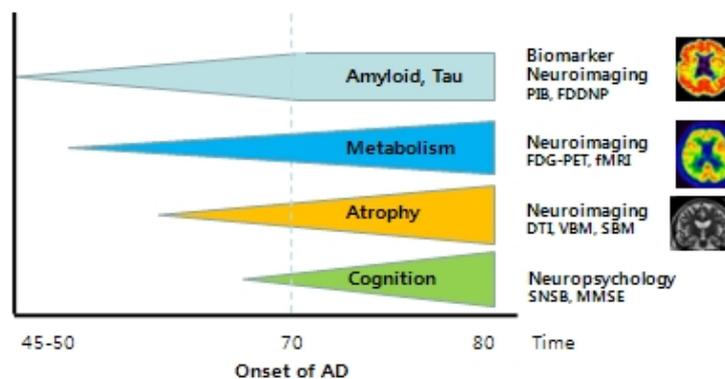
    2. **Efficacy evaluation for new dementia drug is very difficult.**

        1. Acetylcholine esterase inhibitors, developed at the end of '80s, are still the most widely prescribed medication for AD subjects.

2. Due to the slow and relentless progression of dementia, we typically need to recruit a large number of subejcts in a controlled trial (total 3,000 ~ 5,000 person), let alone the long study period (preclinical 8~10 years, clinical 5~6 years).

3. A huge amount of money that covers genetic, neuropsychological, biomedical, neuroimaging approach is needed, as well as multi-center, multi-discipline approach.

3. **Korean elderly are at a greater risk of developing vascular dementia as well as AD.**

   1. The reason of relatively higher prevalence of subcortical ischemic vascular dementia (SIVD) in Korean elderly is not clear.

   2. Rapid increase of vascular risk factors (hypertension, diabetes, dyslipidemia, obesity, smoking etc) in Asian countries might play an important role in onset and course of AD, as well as vascular dementia.

   3. The issue of vascular dementia have greater and more tangible impact in public health perspectives.

4. **More close international collaboration of dementia monitoring and drug development has been started.**

   1. US-ADNI (Alzheimer's Disease Neuroimaging Initiative) has been established in the US in 2005. The purpose of the US-ADNI is detailed monitoring of disease progression of AD and MCI, which is generally considered pre-clinical AD state.

      - Follow up of healthy control 200, MCI 400, AD 200.
      - Result of interim analysis shows the importance of focusing on MCI, thus Early MCI and Late MCIs are to be followed up at ADNI 2.0.
      - Early MCI subjects are additively recruited in ADNI GO (grand opportunity) project.

   2. Launching of Euro-ADNI, Australian ADNI (AIBL), Japan-ADNI followed.

   3. US government (NIH), non-profit organizations like AA (Alzheimer's Association), global pharmaceutical companies, medical instrument companies are very enthusiastic in supporting US-ADNI.

      - Development of sensitive and reliable tool for AD evaluation (early diagnosis and progression monitoring) will greatly save the time and subject number needed to evaluate the efficacy and safety of newly developed anti-dementia drugs.
      - Also, saving of budget in new drug development in public or private sector will be enormous.

- ■ Global pharmaceutical companies may also benefit from expedited approval of anti-dementia drug in several countries due to the common protocol used under world wide ADNI (WW-ADNI) collaboration.
   4. First WW-ADNI meeting was held in Sendai, Japin, in November 2009.

4. **Methods**
   1. **Subjects: 500**
      1. Healthy control: 100
      2. MCI 200 (MCI 100, vascular MCI 100)
      3. Dementia 200 (AD 100, SIVD 100)
      4.

Healthy, SMI aMCI, AD svMCI, SVaD	WMH on MRI		
	minimal	moderate	severe
C O G N I T I O N No cognitive impairment	100		
Mild cognitive impairment	100	50	50
Mild to moderate dementia	100	50	50
Severe dementia			

   2. **Study duration 6 years**
      1. Set up of collaboration centers and preparation (2011. Dec. ~ 2012. Dec.)
      2. Recruitment of subjects (2012. Jan ~ 2013. Dec; 24 months)
      3. Follow up duration for each subjects (36 months)

	BL	6M	12M	18M	24M	30M	36M
NP Test: ADAS-cog, SNSB or CERAD-NP, ADL, CGA-NPI, FBI	O	O	O	O	O	O	O
Biomarkers: Blood, LP, Genetic	O		O		O		O
Neuroimaging: MRI (S,F), FDG PET, Amyloid PET	O	O	O	O	O	O	O

      4. Evaluation of subjects: every 6 months starting from baseline.
   3. **Evaluation items**
      1. Cognition and activities of daily living
         - ■ MMSE, CDR, GDS, CGI-C
         - ■ Detaild NP test: ADAS-Cog, SNSB (Seoul neuropsychological screening battery) or CERAD-NP (K)
         - ■ ADL: ADCS-ADL, Seoul_IADL

- Neurobehavior: NPI, GDS depression, CSDD,
- Computerized assessment: CANTAB or CogState

2. Biological markers
   - Blood markers: amyloid, TTR, etc.
   - Genetic markers: APOE
   - CSF markers: Amyloid 40, 42, Tau, p-Tau

3. Neuroimaging
   - MRI: 3.0T Volumetry, DTI, (some) RS fMRI
   - PET: glucose PET, Amyloid PET

4. **Data acquisition, archiving, and analysis**
   1. Cognition and ADL, other clinical variables: centralization on Web DB
   2. Biomarkers: centralization using land transportation. Detailed protocol to be prepared by biomarker core PI.
   3. Neuroimaging
      - MRI: centralized archiving by uploading to imaging server. Real time quality control by Biomedical Engineering team at Hanyang Univ. Future collaboration with and technical support from US-ADNI being pursued.
      - PET: acquisition and analysis at a few designated centers.

5. **It's high time to launch K-ADNI.**
   1. **Experience and expertise of dementia researchers: Multi-center, multi-discipline dementia registration and clinical study**
      1. CRCD (Clinical Research Centers for Dementia: PI Duk L. Na) has been successfully set up in 2005 supported by Korean Ministry of Health and Welfare. Annual fund 0.6 M U$ for 6 years. Evaluated as the most active and fruitful clinical research center every year among the 11 centers.
      2. Detailed clinical evaluation of dementia patients at 50+ nationwide psychiatry / neurology dementia clinics and research centers using common evaluation protocol.
      3. Centralization of clinical, neuropsychological, and neuroimaging data using online web-database.
      4. Starting from 2006, current registration of dementia subjects exceed 15,000 and more than 7,000 of them are fully evaluated baseline subjects. 2,500 subjects are being followed up annually.
      5. More than 40 clinical studies using current database are being conducted. More than 20 papers are being published annually.
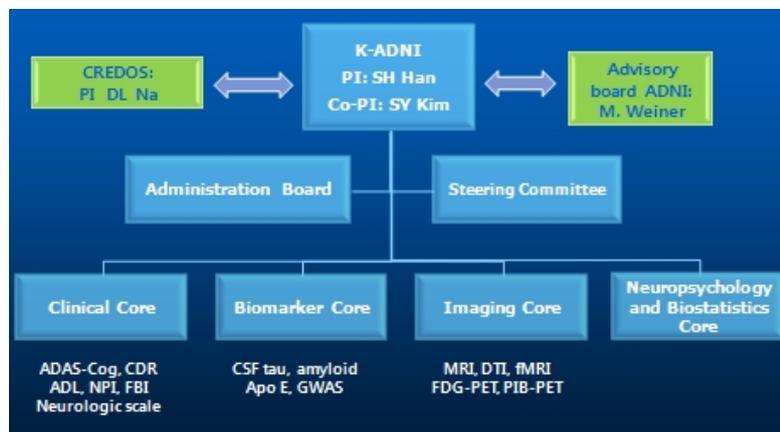   2. **Participation in WW-ADNI**

1. Professor Michael Weiner (UCSF), who is currently the PI of US-ADNI has been invited to Korea in 2009 at the Seoul International Neuroimaging Symposium.
2. Korean dementia researchers and clinicians participated in the first World Wide ADNI meeting in Sendai, Japan, in November 2009. The need, opportunities and obstacles in establishing WW ADNI at a global level have been intensively discussed.
3. Prof. Takeshi Iwatsubo (Tokyo Univ. PI of J-ADNI) also welcoming the establishment of Asian ADNI centers.

3. **Supports from the industry**
   1. Pfizer and GEHC (General Electric Healthcare), which are one of those leading pharmaceutical or medical instrument companies supporting ISAB (industrial scientific advisory board) for US-ADNI, is also interested in supporting K-ADNI establishment.
   2. AA (Alzheimer's Association), an important supporting organization of US-ADNI and WW-ADNI, also looks forward to setting up strong international research collaboration groups in Asia.

4. **K-ADNI Launching Task Force Team**
   1. Established Nov. 2009. PI S.H. Han at Kunkuk Univ., Neurology and Co-PI S.Y. Kim at Asan medical center, Psychiatry.
   2. Clinical Core, Biomarker Core, Imaging Core (MRI and PET), Biostat Core
   3.

5. **Budget estimates**
   1. Estimation of expenses
      - Brain MRI 500 U$, NP test 400 U$, Laboratory tests 300 U$, Amyloid PET 500 U$, LP and workup 200 U$, etc: Total 2,000 U$ / visit
      - Expenses for seven evaluation and administrative fees: 20,000 U$ / subjects * 500 subjects
   2. Grand total 10M U$ (Annal 1.7M U$ * 6 years)

6. **Fund Raising**
    1. Public / Governmental funding: Ministry of Health and Welfare, KHIDI (Korea Health Industry Development Institute) about 20% of total funding
    2. Private or industrial funding
        - KRPIA (Korean Research-based Pharmaceutical Industry Association): 60~70% of total funding
        - KPMA (Korean Pharmaceutical Manufacturers Association): 10% of total funding
        - Individual donations and contributions: 10% of total funding

6. **Expected Results and Merits**
    1. Synergistic Win-Win-Win effect in dementia R&D field
        1. Public / governmental party
            - Large-scale, long term project possible without much increase in public / governmental funding.
            - Much enhanced academic - industrial collaboration
            - Establishment of very efficient R&D model in biomedical and health technology field.
        2. Researcher / Academic party
            - Long term, multi-center, multi-disciplinary research and development possible.
            - Collaboration between pre-clinical, clinical research groups
            - Establishment and consolidation of national and international dementia research network
            - Open use of acquired clinical, biochemical, imaging data for researchers
            - Opportunities for able and young dementia researchers in participating large scale, long-term prospective study
        3. Industrial party
            - Setting up infra-structure of national dementia drug trial network, which also harmonizes with international standards.
            - Mid-size or small pharmaceutical companies can also participate
            - Expedited R&D procedures for new drug development from the bench to the market

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