

Unlocking global collaboration to accelerate innovation for Alzheimer's disease & dementia

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Aim of the Presentation

The primary purpose of this presentation is to suggest ideas-options and generate discussion on an 'action plan' for a multinational initiative - e.g., *IDAD* - to accelerate innovation on Dx and Rx for *chronic brain disorders* such as Alzheimer's disease and dementia.

The Grand Global Challenge of 21st Century

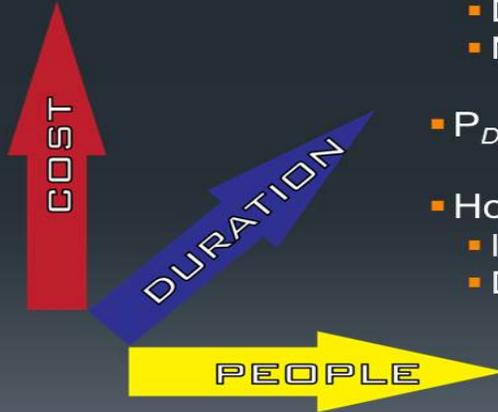
- The 'Mega Problem' for all healthcare systems is the *economic-social-health* burdens on society; the unintended consequence of the ongoing longevity revolution
- There is worldwide recognition for the urgency of a comprehensive multi-nation strategies to reduce the prevalence –'costs' - of chronic brain impairments such as Alzheimer's and dementia
- There is an urgent need for multi-national initiatives – 'public policies' - regarding the: a) expansion of international collaborative R & D, b) acceleration of innovation, c) facilitating-supporting technology transfer biomedicine and, d) harmonization-coordination of global data-sharing rules-approaches-algorithms.

Constituents of the 'Mega-Problem' [P] in an Aging Society

The magnitude [P] is the product of three variables – demographic trends: $P = N \times D \times C$

- N = Represent the numbers of people with for some form of chronic disabling condition – or at elevated risk; where N increases exponentially with aging
- D = Represents increasing duration [in years] of chronic disability; loss of productivity and/or independent functioning of disability [D]
- C = Represents increasing 'costs' of labor-intensive prolonged healthcare; 'costs' includes direct and indirect expenditure - financial as well as psycho-social burdens on care providers.

Problem of Dementia



- Function of:
 - Cost of Care
 - Duration of disability
 - Number of people affected
- $P_{Dementia} = \text{Cost} \times \text{Duration} \times \text{People}$
- How to balance?
 - Invest to modify “C”, “D” or “P”
 - Develop rationing plans

Vision for Unified-Global Struggle

The global scale of [P] - the pending healthcare crisis - mandates a forward looking action plan to harmonize a multi-nation attack on [P].

The central premise for a decade- long multinational endeavor is - ***chronic brain disability is a major global social-economic challenge***; which will grow exponentially with the projected demographic trends. -

Multi-National Strategic Goal

The challenges for a well-coordinate assault are:

- Formulate the framework for global policies to enable-accelerate multi-national collaborative R & D on early detection [Dx] and prevention [Rx] of disabling conditions
- Plan-launch a decade-long initiative is to mobilize multinational efforts to:
 - 1) develop new knowledge,
 - 2) expand R & D resources/technical capabilities
- Enabling society to **reduce the prevalence of Alzheimer's disease (AD), Traumatic Brain Injury (TBI) and other Chronic Brain Disorders (CBD) that affect memory, movement, and mood; by 50% within five years and by 75% within ten-years** –
 - *[A modest delay of five years in the onset of brain disability will reduce the cost and prevalence of these chronic conditions by half]*

Rationale Bold Strategic Goal

- Articulate a well-defined clear cut target for coordinated effort by all stakeholders
- Harmonize thinking & effort
- Mobilize resource
- Provide metric for measuring progress
- Identify significant barriers to progress and strategies to surmount these impediments
- Aim for a significant 'Health-Economic' outcome-impact e.g., A modest delay of five-years in the onset of disability will reduce prevalence and costs of healthcare by 50%

Specific Aims of a Global Strategic Goal

A multi-national strategic goal should include:

- critical re-evaluation of well-accepted traditional concepts of R & D on Dx-Rx and healthcare services
- ideas-plans for expanded research investments
- approaches-models for coordinated strategies to address the big data challenges, and
- economic-financial analysis-documentation for the massive implications of “Alzheimer’s Problem” for economic growth member countries
- exploration of models for partnerships to facilitate the translation of biomedical innovation for Alzheimer’s disease

Scientific-Technical Challenges

- Presently no country, company or entity has the capability to attain the strategic goal of preventing chronic brain disorders
- The strategic goal of delaying the onset or preventing chronic brain impairments within a decade will require the discovery-development-validation of new a) scientific knowledge and b) technologies for early detection- identification [Dx] of asymptomatic people and interventions [Rx] that modify disease progression
- The specific aim for multi-national initiative is to develop scientific-technical capabilities for accurate prediction of people at elevated risk in asymptomatic populations.

Critical Unifying Scientific Question

The primary challenge for a multi-national decade-long collaborative R & D initiative on '*Prevention*' is:

The discover-validate of the *earliest* and *smallest* measurable cluster or combination of changes in performance-biomarkers-imaging in asymptomatic population – measures that can serve as *accurate prognostic* indicators of pending chronic brain impairment or dementia.

The availability of such technologies will drastically reduce the *cost* and *duration* of 'disease modifying' or 'prevention' trial

Major Barriers to the Strategic Goal

Decade-long Strategic Goal of delaying the onset of disability – '*Prevention*' - is an attainable target for a multi-national initiative; however, we must surmount an array of impediments:

- ***Scientific-technical:*** New conceptual models based on systems biology for complex disorders – scientific-technical knowledge base for new Dx and Rx
- ***Infrastructure-research resources:*** 'Mega-Database' as a shared multinational R & D resource/core facility; computational methods/algorithm for data-mining and 'knowledge extraction
- ***Administrative-organizational:*** Governance, rules, procedures and agreements re: data management-sharing, publication and credits; planning & execution of long-duration [decades long] large-scale multi-national/site prevention studies/trials
- ***Regulatory-legal-ethical:*** regulatory requirements for 'outcome measure' of efficacy for prevention trials with asymptomatic subjects/populations; IP licensing agreements/revenue-sharing in multi-national studies
- ***Financial:*** New models for sustained [decades-long] funding/financing multi-national 'collaborative R & D projects – international 'big science' initiatives

The Scientific Aims

- Discover, Develop and Validate:
 1. Technologies, tools and algorithms for early and accurate *detection* of not only people with the disease but also asymptomatic individuals at elevated risk for various forms of memory disorders
 - *behavioral assessments, family history, genetics, biomarkers, neuroimaging and computational techniques.*
 2. A wide range of *interventions* to preserve and/or restore normal neural function and to maintain independent functioning for as long as possible.
 - *Includes not only drugs and biologics, but also behavioral, lifestyle, and applications of technologies in the home or care environment.*

Challenges Confronting Prevention Initiatives

- Validation of methods for detecting asymptomatic people with elevated risk early in the pre-clinical stages disease
 - Continued biomarker, imaging, and cognitive assessment development
 - Development of additional assessment technologies, e.g. for behavior and movement
- Lack of validated therapeutic targets
- Need for new conceptual models
- Complexities for randomized prevention trials
- Need for improved coordination among all Alzheimer's related activities
- Long time-lag for research funding
 - Lack of quick-response funding for breakthrough ideas
 - Difficulties in establishing public-private-international efforts
 - New models for financing clinical research
- Other issues including patent life, drug marketing exclusivity and reimbursement

International Database on Aging and Dementia [IDAD] Project

- **Aim**
 - Assemble large, geographically-dispersed, well-characterized, population-based, cohorts of study participants
 - Continuum from asymptomatic, elevated-risk to early impairment
 - Validate biological, genetic and behavioral biomarkers as well as other characteristics that may predict AD
 - Resource will be pivotal for “prevention” trial recruitment, health services research, public health policy planning
- **Tasks**
 - Establish a network-consortia of ongoing healthy aging and dementia cohort studies: ONGOING/EXPANDING
 - Implement the use of standardized computer-based cognitive assessments and other technology applications among consortia projects
 - Greater frequency of data capture & issue “subject burden”
 - Emphasis on use of technology to lower costs
 - Provide a federated global database and modelbase available for consortia members and non-members:

Potential Cohorts/Databases

Ongoing longitudinal studies provide an excellent foundation on which to build the proposed IDAD; these ongoing efforts could provide the basic elements needed for a large multi-national cohort. The design and operation of a multi-national shared resource – IDAD - should take into account the complexity and challenges to new studies stemming from differences in histories, cultures, and healthcare delivery systems in participating centers that shaped previous studies.

Potential Cohorts/Databases Continue

- Baltimore Longitudinal Study on Aging
- Framingham Heart Study
- Mayo Clinic Study,
- NYU Center for Brain Health Study
- The Rotterdam Study, a longitudinal study of chronic disease
- Alzheimer's Disease Neuroimaging Initiative (ADNI) and Euro-ADNI
- The Cardiovascular Health Study (CHS)
- Multi-domain Alzheimer Preventive study by the 'Centre Hospitalier Universitaire de Toulouse', Bordeaux, Limoges, and Montpellier,
- The German Competence Network on Dementias
- The Consortium of Canadian Centers for Clinical Cognitive Research (C5R).
- Canada (the Canadian Longitudinal Study on Aging [CLSA])
- Spanish study of environmental exposure on neural development.
- The Genome-Wide Association Studies (GWAS)
- The European Community Concerted Action on the Epidemiology and Prevention of Dementia Group.

Potential Cohorts/Databases Continue

- The Dominantly Inherited Alzheimer Network (DIAN) - individuals at-risk for autosomal dominant AD (ADAD).
- The European Prospective Investigation into Cancer and Nutrition - Cognition Consortium (EPI-COG)
- The Alzheimer's Prevention Initiative (API)
- The Wisconsin Registry for Alzheimer's Prevention (WRAP) and the Israeli Registry for Alzheimer's Prevention (IRAP)
- Global Alzheimer's Association Interactive Network – GAAIN
- Orange County Vital Aging Program (OCVAP)
- Barcelona-Pittsburg Longitudinal Study
- Alzheimer's Disease Neuroimaging Initiative (ADNI) and its follow-up study, ADNI-II; Australia (Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing).
- Alzheimer's Disease Research Centers (ADRC),
- Alzheimer's Disease Cooperative Study (ADCS),
- National Research Bank for Genetic Studies of Alzheimer's Disease,
- National Alzheimer's Coordinating Center (NACC),
- National Cell Repository for Alzheimer's Disease (NCRAD)

Potential Core Functions

- Administrative [Financial-Legal-Business management]
- Clinical-Scientific Coordination
- Biostatistics-Informatics-Computational capabilities
- Database Management/Warehousing
- Genetics [Cell/DNA Repository –Genotyping]
- Biomarkers
- Neuroimaging {PET/MRI Pre-Processing}
- Behavioral Assessment
- Instrument Development
- Neuropathology
- Electronic Medical Records
- Demographics
- Health Services
- Health Economics
- Repositories/Tissue/Fluids/Genetic/Banking
- Ethics/Subject Safety/Privacy/Informed Consent
- International /Institutional Review Boards [I-IRB]
- Publications/Information/Communications
- Legal/IP/
- Commercialization/Industry Liaison
- Others

Potential Applications-Benefits of Big Data - IDAD

The availability of IDAD i.e., database that provides longitudinal information on large cohorts, will provide a *significant 'add-value'* to many ongoing or future studies requiring a well characterized research subject that reflect the diversity in the general population. The following are some example:

- Genomics
- Biomarkers
- Cognitive Assessment
- Research on Discovery-Validation of Dx Technologies for Detection of People at Risk
- Health Economics & Psycho-social Studies on: Health Services, Cost-Burdens of Care
- Reduce the Cost and increase the Efficiency of Clinical Studies
- Provide a Resource for Technological Innovations
- Provide Stability to a Healthcare Resource and
- Ensure Future Recovery of Value from Investment in Resource Development

History of R & D Capacity Building: 1978-Present

- 1978 – Beginnings of *Alzheimer's & Brain Aging* research programs at National Institute on Aging/NIH – promoting: a) formulation of diagnostic criteria, b) development- validation of clinical assessment tools and c) creation of research *infrastructure to support longitudinal clinical studies*
- 1984-2004 – Evolution of the concept of 'shared-resource'/collaborative research: Alzheimer's Disease Research Centers (ADRC), Consortium to Establish a Registry for Alzheimer's Disease (CERAD), Alzheimer's Disease Cooperative Study (ADCS), National Research Bank for Genetic Studies of Alzheimer's Disease, National Alzheimer's Coordinating Center (NACC), National Cell Repository for Alzheimer's Disease (NCRAD), and finally the Alzheimer's Disease Neuroimaging Initiative (ADNI) and other longitudinal population based initiatives.

History of R & D Capacity Building: 1978-Present – [continue]

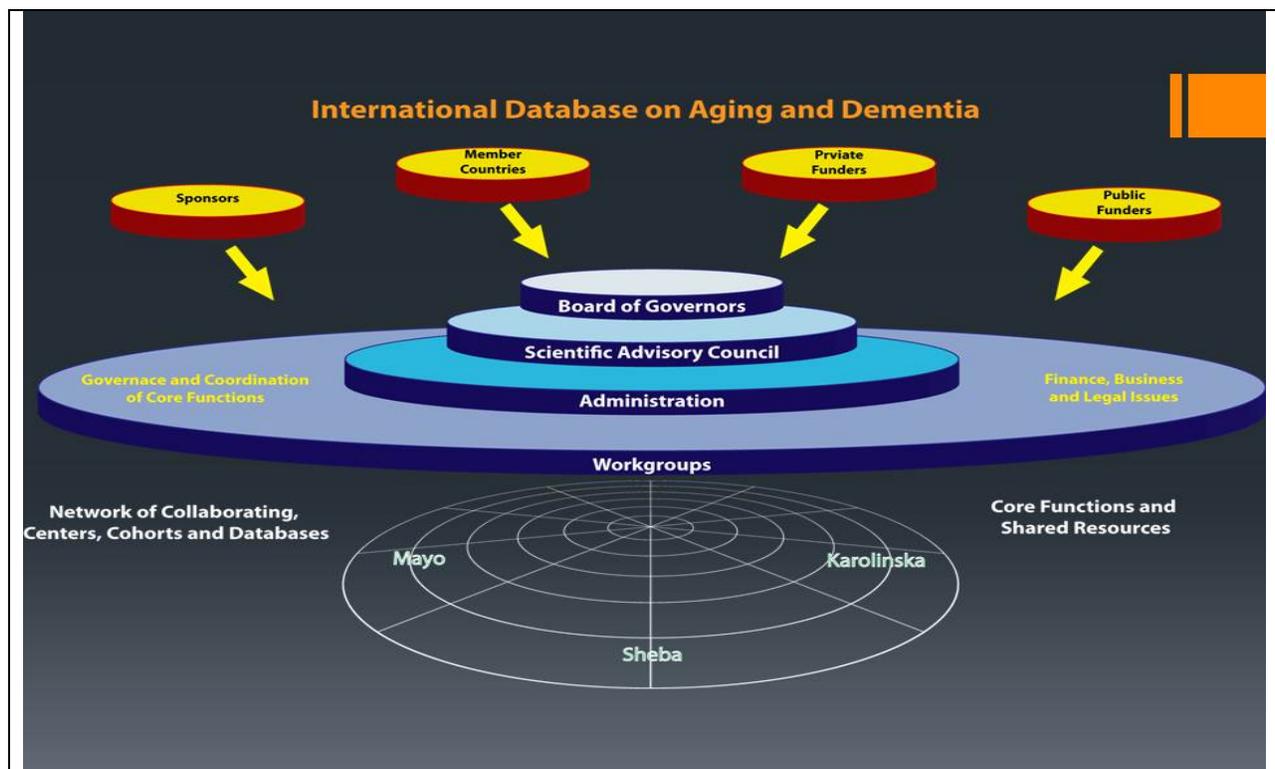
- Early efforts [1984-2004] focused on the creation of *infrastructures* and building *capabilities for clinical studies-trials on people with the disease*.
- 2004- Present - The focus of the field shifted towards research on *people without the symptoms of the disease*, but at elevated risk. –disease progression. Thus the current challenge is to build the appropriate infrastructure to address the newly emerging needs of the field regarding R & D on disease progression and prevention.

'Big Data' – Construction, Governance & Financing

International Database for Longitudinal Studies on Healthy Aging & Pre-Clinical Dementia [IDAD]

Very large population-based, genetically diverse, cohorts are essential resources for validating new technologies for accurate identification of asymptomatic people [pre-clinical stages] at elevated risk for AD and other CBDs – thus the need for 'Big-data' and 'Knowledge-mining' capabilities

- The unique clinical features of Alzheimer syndrome, TBI or CBDs will require a *different type of infrastructure, which does not exist; a new research resource that can provide a comprehensive database on well-characterized cohorts*
- Existing population-based cohorts and/or studies could offer valuable data, *however*, these do not individually fulfill all of the specific needs of: a) *prospective validation studies*, b) developing new computational algorithms/models, which will require large databases from varied sources and domains of measurements [e.g., biomarkers, genetic, behavioral, imaging and other information on co-morbid conditions], in order to discover/establish probability profiles for predicting the relative risks for memory disorders/dementia in asymptomatic populations and c) furthering the fundamental understanding of the heterogeneity in the prevalence-incidence of AD as well as the knowledge about people at greatest risk for developing AD



'Big Data' – Construction, Governance & Financing

International Database for Longitudinal Studies on Healthy Aging & Pre-Clinical Dementia [IDAD] - [Continue]

- The challenge to accelerate the discovery-validation of new: *scientific knowledge, technologies and computational algorithms* for accurate identification of asymptomatic people at elevated risk for AD mandated the creation of the proposed comprehensive R & D infrastructure
- Current resources, established cohorts and ongoing longitudinal studies are fragmented and inadequate, due to: a) relatively small sample sizes and, b) lack of guaranty for long-term support/funding required to underwrite the longevity of cohorts
- One of the critical needs to advance research on strategies to delay the onset of chronic brain disability [or prevention], is the availability of a comprehensive infrastructure for long-duration prospective studies to: a) validate putative biomarkers prognostic capabilities or accuracy and/or b) determine the influence of potential risk factors e.g., genetic, lifestyle, and environmental factors on the clinical course of the syndrome.

Critical Challenges for Constructing IDAD

The illustrative list of challenges-questions regarding the: *design, management* and long-term *financing* for a multi-national database includes:

- **Issue # 1** - *How to coalesce-harmonize various efforts, regarding well-established population based cohorts or databases, underway around the globe without interfering with existing studies?*
- **Issue # 2** – *How to create a multi-purpose multi-national core facility; a shared R & D resource that could serve divers needs such as those of both epidemiologic studies and prevention trials?*
- **Issue # 3** – *What are some of the different models for constructing a Multi-national Core Facility to achieve the dual goals of establishing a large population-based registry and facilitating clinical trials?*
- **Issue # 4** – *How to bring about a paradigm-shift in discovery-development-validation of therapies for prevention – a change in thinking towards a public health model?*

Critical Challenges for Constructing IDAD Continue

- **Issue # 5** - What to measure - which domains of data should constitute the hard core of the database?
- **Issue # 6** – Who to include – which cohorts are essential to the Multi-national Core Facility?
- **Issue # 7** – How, when and where data gathering for multi-national database occur?
- **Issue # 8** – How will questions regarding data management be resolves? Should data be stored in a centralized location, or at multiple, decentralized locations? Should blood and tissue be stored in a central repository?
- **Issue # 9** – Where or who are some of the potential participating sites – collaborating partners in establishing such a international research resource?
- **Issue # 10** – What would be the framework for managing this multi-national Core Facility?
- **Issue # 11** – What would be the structure and process for sharing information that transcends current competitive practices in industry and academia?

Critical Challenges for Constructing IDAD Continue

- **Issue #12** – How IDAD could accommodate the need for share computational resources and modeling approaches?
- **Issue # 13** – How to train community physicians to identify early warning signs and intervene appropriately when patients present with a memory concern? Could a useful model be developed for using community physicians as important portals of data to an International Core Facility? What will be required to develop-validate web based: a) cognitive assessment tools for physicians and b) self-assessment tools for the public, which would enable community cognitive screening services?
- **Issue # 14** – How could an IDAD be financed; what are some of the different models for long-term sustained support for such a multi-national enterprise?

Tasks - Measures of Progress

- Agreement on a process to develop common standards and best practices for data deposit, management, access and sharing
- Specifications of an *efficient governance and management system* for the operating-administering such an international *public-private enterprise*
- Development of a *mechanism/model for long-term financing* this multi-national resource.

Specific mileposts of the project

- *Concept Review & Project Planning*
- Create an international oversight and governance mechanism for administering such an undertaking; convening an international *Advisory Board*, establishing a *management team* and organize *WGs* on governance and financing
- Review and assess the major data series that can be collected or combined to standardized formats, and deposited, codified and made accessible for truly international comparative purposes. Assemble a comprehensive list of all ongoing databases [a 'registry of registries']
- Start the process of evaluating options for coordinating/integrating existing database and assessing the needs for additional types of data. The development of a comprehensive
- IDAD will require thorough assessment of existing cohorts with the aim of integrating, harmonizing and standardizing [whenever possible] all ongoing longitudinal databases regarding different domains of measurements e.g., behavioral, biological, life-style, genetics, neuroimaging, biomarker and other healthcare or services information.

Specific mileposts of the project continue

- Forge an international agreement on standards and best practices for data deposit, management, access and sharing; including decisions about the policies and rules that govern access to the shared-resources. Start the process of creating a network of collaborating investigators/databases to launch multi-site collaborative effort to develop/refine development computer-based assessments for data gathering, including assessments of behavioral and/or memory changes associated with aging that are appropriate for broad use in non-expert settings.
- Development of computational methods/algorithms for health data mining, simulation or modeling
- Start implementing recommendations from WG into the ongoing study of WRAPIRAP-Mayo by incorporating ideas re: study sampling design, other sites, measurements, uniform standardized assessments, assembly of larger cohort of well-characterized, asymptomatic volunteers at risk for the disease; other subjects who would be willing to participate in trials to validate biomarkers and test preventive treatments.

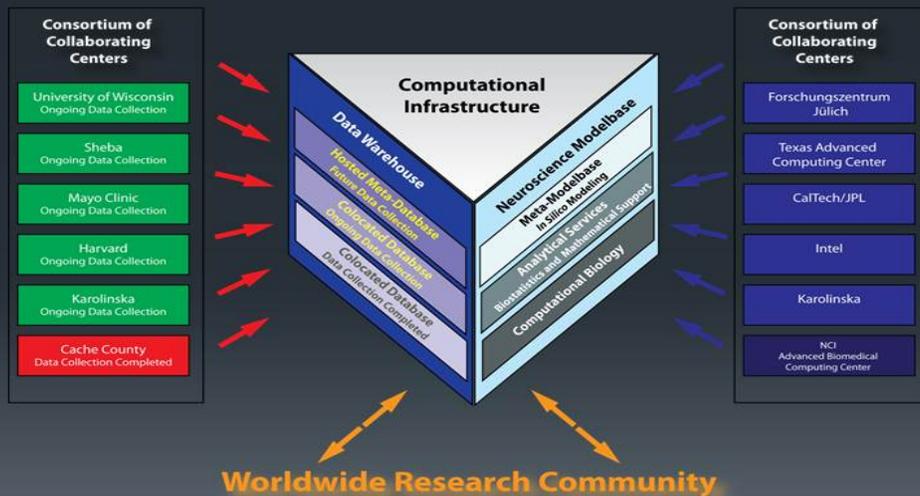
Specific mileposts of the project continue

- The project will continue refining the implementation plans recommended by the WG.
- The pilot phase of the project will deliver a small scale prototype database designed to evolve by continuous refinements on the basis recommendations by specialized workgroups to continue the development process. For example, various workgroups will focus on such issues as; additional resources/infrastructure required; domains to be studied; additional types of data and biological samples that will be needed; conditions for collecting these samples; refinement of the computational biology required; evaluation of computer-analyses existing databases; combing the literature more systematically and cataloguing the designs and executions of existing studies; determine how to piggyback on other studies or databases; governance framework for the collaboration; administrative structure, systematic public education effort, and funding strategies.

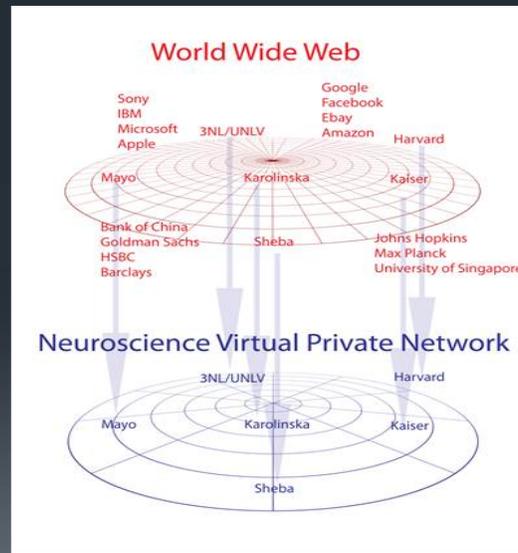
German Biological Resources Centers [GBRCN]
 Braunschweig, Germany
www.GBRCN.org

- **Problem:** The complexity of data collection, distribution and use of living biological material demands the *coordination* and *sharing of activities*. The task of ex-situ conservation is enormous and exceeds the technical potential of an individual collection in any individual country.
- **Aim:** Enhance the efficiency in collections of laboratory held, living biological material, by co-coordinating and driving activities to meet user needs. A network designed to accommodate the future needs of biotechnology and biomedicine
- **Illustrative Example:** The value of networking activities, developing common approaches and enhancing coverage of available organisms and information to meet user requirements
- The present partnership brings together 15 countries with the World Federation for Culture Collections (WFCC), a global network and regional networks, the European Culture Collections' Organization (ECCO) and the Asian Consortium for Microorganisms (ACM).

International Database on Aging and Dementia Project



International Database on Aging and Dementia Project



Systems Approach

Ludwig von Bertalanffy, ascribed as the founder of general systems theory, wrote:

"Modern science is characterized by its ever-increasing specialization, necessitated by the enormous amount of data, the complexity of techniques and of theoretical structures within every field. Thus science is split into innumerable disciplines continually generating new sub-disciplines. In consequence, the physicist, the biologist, the psychologist and the social scientist are, so to speak, encapsulated in their private universes, and it is difficult to get word from one cocoon to the other."



- Thank you...