TORONTO DEMENTIA RESEARCH ALLIANCE

Barry D. Greenberg, Ph.D.
bgreenbe@uhnresearch.ca
Director, Neuroscience Drug Discovery and Development, UHN
Director of Strategy, Toronto Dementia Research Alliance

UNIVERSITY OF TORONTO
FACULTY OF MEDICINE

TDRA:
Centre for Addiction and Mental Health
Baycrest/Rotman Research Institute
Sunnybrook Health Sciences Center
University Health Network
St. Michael's Hospital
University of Toronto

ADC – 24 Sep 2011

Creation of a Toronto-Wide Centre for Dementia Research

Toronto Dementia Research Alliance

TDRA - History

- **Brain Imaging and Biomarker Alliance – initial meeting with representatives of UHN, Baycrest, Sunnybrook and CRND on 16 September 2009**
- **Development of Provincial, national and international initiatives providing significant funding potential and collaborative opportunities**
- **Matured into effort to position ourselves proactively as a Canadian ADRC-type Centre of Excellence in research on dementia, co-morbidities, and co-occurring, contributory, underlying disorders**
- **Inclusion of CAMH, St. Mike's – all of the UT-affiliated memory clinics**
- **Division-based representation added to Core Team – beginnings of matrix structure to cover all relevant disciplines**
- **Vision and capabilities presented at NIA reverse-site visit, AAN meeting in Toronto, April 2010**
- **Seed funding secured from University and participating hospitals, September 2010**
- **First R01 submitted to NIH Epigenetics Roadmap, September 2010**
- **Strategy retreat for Executive and Steering Committees, December 2010, culminating in completion of formal strategy document, February 2011 *(available on request)***
- **Cornerstone contributor to Ontario Brain Institute application on neurodegeneration, August 2011**

Vision:
Toronto Centre for Research on Cognitive Disorders

- Cognitive and related disorders: Dementia, movement disorders, mood and psychiatric disorders, cerebrovascular disease, metabolic disorders
  - Preclinical basic and applied research including animal modeling focused on disease mechanisms and therapeutic targets
  - Genetic/epigenetic risk factor identification, novel gene discovery, pharmacogenetics, novel target identification and drug discovery
  - Biological fluid, image- and ocular-based biomarker analyses across continuum of preclinical models, prodromal and clinical disease states of increasing severity
  - Integration of multi-modal imaging relationships - brain function, structure, pathology, metabolism, neural network characterization
  - Focus on prodromal disease

Focus on prodromal disease

- Identification and treatment of patients at risk
  - Development of novel psychometrics in pre-symptomatic and early dementia
  - Cross-validation of relationships among pre-symptomatic and clinical dementias with co-occurring/contributory/underlying progressive disorders
- Our most valuable asset: Robust patient cohorts for longitudinal and cross-sectional studies
  - 2000 new patients/yr, 5000 follow-up in memory clinics
  - Association under development with additional academic centers, neurological disease clinics, and Ontario Health Study
  - Availability of dominant mutation-carrying pedigrees for DIAN-esque studies
    - **AD**: Several known PS1 and APP families. Currently following 28 cases with EOFAD age of onset $\leq$ 55; 36 cases with EOFAD age of onset 56-65
    - **FTD**: Four known PRGN families. Currently following 9 symptomatic carriers, 8 asymptomatic carriers, 13 non-carriers
    - **PD**: Five known LRRK2 families. Currently following 7 symptomatic carriers, 23 asymptomatic carriers, 46 non-carriers

Co-morbidities and Co-occurring Disorders

Major Programmatic Strengths include:

- Multi-institutional Stroke Centre (Sunnybrook, UHN, SMH)
  - Emphasis on Vascular Cognitive Impairment
- Fronto-Temporal Dementia program (Baycrest)
- Parkinson/Movement Disorders centre (multiple)
- Mood Disorders Psychopharmacology Unit (UHN)
- Psychiatric Disorders clinic and research centre (CAMH)
- Strengths in all relevant therapeutic areas (all U of T hospitals)
  - i.e. Cardiovascular, metabolic disorders, etc.

Innovations, Opportunities and Impacts

- (Some) Additional innovations and opportunities:
  - Longitudinal and cross-sectional studies on ocular pathology
  - Epigenetic analyses – cross-correlation with disease progression
  - Neuroinformatics and neural network modeling
  - Pioneering studies in human cognition
  - Cerebrovascular antecedent risk factors, revascularization treatment potential
  - Novel surgical & clinical approaches for treatment/hypothesis generation, i.e. DBS
- Impacts on:
  - Cross-validation in preclinical models and humans of novel sets of genetic markers, biomarkers, brain function and clinical assessments
  - Clinical trial design and responder analyses by supporting patient sub-group segregation to identify those with better chances of responding to selected therapies

U of T - Dementia Research and Clinical Care

- High ranking research university, particular strengths in Neuroscience
  - Genetics, to cellular and animal models, to brain networks
  - Cognitive Neuroscience, frontal lobes, memory
  - >500 basic and clinical neuroscientists
- Strengths in neuroimaging and image analysis
  - sMRI, fMRI, PET, MEG, SPECT, DTI with associated informatics
  - Pipeline for analyzing co-morbid vascular and AD, other co-occurring/underlying disorders, population-based studies
- Clinical care
  - Largest group of Behavioral Neurologists and Geriatric Psychiatrists in Canada

U of T – Clinical Research in Dementia

- Active participant in North American and international consortia
  - ADC MCI study, ADNI and ADNI-GO
- Participation in international clinical trials
- Sunnybrook Dementia study
  - 15-year ongoing longitudinal observational study
  - Archive of > 1000 patients with neurodegenerative dementias, MRI, SPECT, detailed neurobehavior
  - > 100 publications, autopsies in 130

CAMH PET Program

Mood disorders, Schizophrenia, Addictions, PD, AD

- 28 PET radiotracers for human imaging
  - 12 were 1st use worldwide; 10 1st use in Canada
  - 4 new approaches for imaging AD:

    Plaques, neuroinflammation, metals, cholinergic system
- Radiochemistry facilities
  - Patented ^{11}C-technology,
  - 17 and 30 MeV cyclotrons operational
  - 1 head-only scanner (HRRT) and 1 PET-CT
- Expansion highlights include:
  - fMRI, small animal imaging, new GMP labs

Ontario Health Study

- Launched in September 2010. Population-wide health study aimed at investigating factors that influence risk for development of cancer, cardiovascular, metabolic, respiratory and neurodegenerative disease.
- Funders: Ontario Institute for Cancer Research, Cancer Care Ontario, Public Health Ontario , Canadian Partnership Against Cancer.
- Will be the largest volunteer cohort ever conducted globally
  - Targeting the 9.5 million Ontarians over the age of 18, to be followed for 20 years.
  - >35,000 enrolled as of June 2011.
- Nested data collection strategy
  - "Thin" data collection on all volunteers (annual survey).
  - "Thin-Plus" on >100,000 includes biosample collection.
  - "Thick" on >40,000 including detailed physical and cognitive assessments every 4-5 years.
- Scientific organization:
  - 31Discipline-specific Working Groups . Strong interactions through Science Committee for cross-assessments to elucidate complex interplay of factors that underlie the development of common diseases and co-morbidities.
  - Relevant to TDRA: Aging/Gerontology, Cardiovascular, Cognition, Endocrinology, Genomics/Molecular Epidemiology, Imaging, Neurology, Ophthalmology.
- Secure informatics platform and linked biorepository (blood, saliva), ethics approvals in place.
- *Science information package available by request.*

TDRA ⟷ Ontario Health Study

- Cross-relationships with TDRA
  - TDRA Core Team members participate in Cognition, Endocrinology, Neurology and Imaging Working Groups, and the OHS Science Committee.
  - OHS Science Officer is a member of the TDRA Core Team.
  - Fosters interactions with leading scientists throughout Ontario while facilitating integration of studies related to dementia and co-occurring disorders/co-morbidities, with access to cross-generational cohorts.
- Example: Cognitive Working Group
  - Developing novel computerized population-based battery to identify the initiation and progression of decline over time, undergoing validation. Components of Cogstate under exploration.
  - Links to memory clinics for deeper assessments will be possible when warranted for capturing patients in early stages of decline, pending consent.
- Informatics platform and biorepository
  - Biological samples and archived data will be available to qualified applicants for independently funded sub-studies.
  - Plans under development for 6000 longitudinal MRIs at 5 year intervals, pending funding.
  - Possibility for linking informatics platform and biorepository with TDRA clinics.
  - Obvious objective: development of powerful datasets to identify key risk factors and correlates for the onset of dementia, enabling targeted patient stratification for clinical research and therapeutic trials.

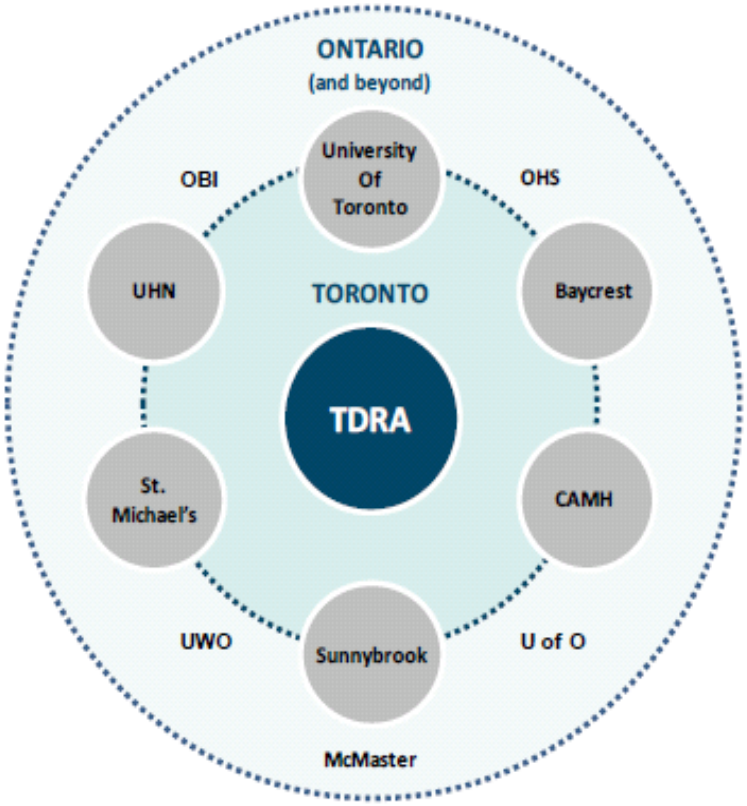
Ontario Brain Institute

- Launched November 2010. Not-for-profit corporation funded by the Government of Ontario, established to become an internationally recognized center of excellence in brain research, translation and innovation.
- Initiating, funding, promoting and stimulating brain research, education and training.
- Brings together Ontario's leading basic and clinical neuroscientists for large multi-institutional collaborations and creation of cross-cutting platforms.
- Focus is on clinical neuroscience research.
- Outcomes designed for translation into clinical applications and commercialization opportunities related to early diagnosis, treatment, management and prevention of brain disorders across the life spectrum.

TDRA ⟷ Ontario Brain Institute

- Discussions to date relevant to TDRA:
  - Workshop on cross-assessments among clinics focused on AD, PD, DLB, FTD, vascular dementia, stroke, from medical research institutions within Toronto, London, Ottawa, Hamilton, Kingston, etc., to begin developing worthwhile and well-integrated project applications. A first time "gathering".
  - Establishment of a province-wide informatics system as a resource for electronic patient records and data archiving, including brain imaging data files, that will facilitate efforts throughout Ontario.
  - Linkages with commercial co-funders/collaborators.
  - Facilitation of multi-institutional ethics approval processes.
  - *Obvious synergies among TDRA, OBI and OHS.*

Organizational Vision



Toronto-based Institutions in the TDRA

Examples of external institutions (Ontario and beyond) with which the TDRA aims to partner

TDRA Aims

- Function as population-based translational research endeavor aimed at improving patient care and supporting discovery science.
- Become a magnet for dementia research, attracting world-class scientists and trainees.
- Capitalize on emerging funding opportunities from the public and private sectors.
- Establish appropriate infrastructure and processes to become an attractive hub for industry- and investigator-initiated clinical trials.
- Position itself proactively to grow into a comprehensive center of excellence in cognitive disorders.
- Provide a forum for scientific exchange, strengthening collaborations among Toronto's research community, and with other Provincial, national and international academic centers.

TDRA - Outcomes

- An ADRC-type COE in Toronto will create innovative, integrated and synergistic research programs extending from basic to clinical research, and POC for novel therapeutic & diagnostic agents in preclinical models and early-phase clinical trials
  - Synergies between basic research on disease targets and mechanisms, with observations in clinical trial and population-based human studies
  - Cross-sectional and longitudinal multi-disciplinary studies
  - Participation in the developing initiative-driven collaborative landscape for addressing dementia, competing/participating on the global stage
  - Broad interactions with additional academic centers and international collaborations
  - Cross-sector funding – governmental, voluntary, industrial, private
  - Improved patient care


Toronto Centre for Research on Cognitive Disorders

TDRA – Management Team

September 2011

- **Executive Committee** - Interim Director, Tony Lang – UHN, University of Toronto
  - Barry Greenberg – TDRA, Director of Strategy
  - Ellie Aghdassi – TDRA Coordinator
  - Randy McIntosh – Baycrest
  - Sandra Black – Sunnybrook
  - Bruce Pollock – CAMH
  - Art Slutsky – St. Mike's
- **Core Team** – Chair, Barry Greenberg
  - TDRA: Ellie Aghdassi, TDRA Coordinator
  - University of Toronto Neurology: Tony Lang
  - UHN: Ron Keren, David Tang-Wai, Mary Pat McAndrews, Roger McIntyre, Carmella Tartaglia
  - Baycrest: Lisa Goos
  - Sunnybrook: Mario Masellis
  - CAMH: Aristotle Voineskos
  - St. Mike's: David Munoz
  - Behavioural Neurology: Morris Freedman
  - University of Toronto Stroke Program: Jennifer Breaton
  - Ontario Health Study: Kelly McDonald
  - CRND: Howard Mount
  - Geriatric Medicine: Gary Naglie

Operations

- Ongoing Working Groups
  - Academic harmonization
  - Clinical harmonization
  - Imaging harmonization
  - Research projects and funding

- Formation of Scientific Advisory Committee
  - Ensure alignment of research activities with scientific mission
  - Oversee and advise on projects supported by TDRA
  - Facilitate establishment and solidify inter-institutional alliances
  - Recommend feasible trajectory for commercialization of IP

University of Toronto – Neuroscience

- Integrating neuroscience to link and promote educational and research activities at UT and its affiliated teaching hospitals/research institutes.
  - 231 Faculty, 191 Students, 141 Postdocs

Academic Centres

- Toronto, St. George, Scarborough & Mississauga campuses
- Centre for Research in Neurodegenerative Diseases
- MaRS
- Samuel Lunenfeld Research Institute
- McLaughlin Centre for Molecular Medicine
- McEwen Centre for Regenerative Medicine

Medical Research Institutes

- University Health Network
  - Toronto Western Research Institute
  - Ontario Cancer Institute (PMH)
  - Toronto General Research Institute
  - Toronto Rehabilitation Institute
- Sunnybrook Health Sciences Centre
- Centre for Addiction & Mental Health
- Baycrest
- St. Michael's Hospital
- Hospital for Sick Children
- Bloorview Kids Rehab

Opportunity: Research Funding through Provincial, National, & International initiatives

- Canadian initiatives
  - ICRSAD (CIHR - International Collaborative Research Strategy for AD)
  - Ontario Brain Institute
  - Ontario Health Study; partnered-studies for independent funding
  - CDAN? Brain Canada?
- Interactions with US-based initiatives
  - PAD2020 (Prevent AD by 2020)
  - NIA, NIH, Alzheimer's Association
- Opens doors for novel cross-sector funding
  - Government, Industry, Foundations, Private donors
    - Currently under consideration: NIH, CIHR, Alzheimer's Association-US
    - Ministry of Research and Innovation
    - Several pharmaceutical companies in contact

What will happen over the next several years?

- Improved symptomatic therapies remain critical - of most immediate value to patients and their caregivers. But these will not stem the tide of the disease.
- Delay for disease modification and prevention is untenable
  - 5 million Americans are currently afflicted with AD.
  - Will increase by 50% in 20 years, 300% by 2050
  - Cost in US: currently $100B/yr, $20T over next 40 yrs, $1T/yr by 2050
  - Projection: 24% Chinese population afflicted by 2050 = >300 million
- Feasibility for DM and prevention exist in principle. Barriers must be broken.
  - No more "Business as Usual"
  - Collaborative national and international initiatives, cross-sector alliances, national registries, changes to regulatory and intellectual property policies, new legislation
- The only path to success in an acceptable time frame