Clinical Trials: Targets/Biomarkers/Outcomes/Co-morbidities

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Toronto Dementia Research Alliance
U of Toronto-Dementia Research

- Clinical Strengths: *largest group of Behavioural Neurologists in Canada (7 and growing) and Geriatric Psychiatrists (>12)-Integrated approach*
- Strong Cognitive Neuroscience and leading in brain network analyses, frontal lobes, memory
- Strong in Neuroimaging— *functional and structural; pipeline for analyzing comorbid vascular and AD*
- Participated in ADC MCI study, and currently in ADNI and ADNI-GO
- Participation in international clinical trials eg monoclonal antibodies phase 1, 2, 3
- Toronto alliance could increase size and scope of clinical trials for novel compounds from proof of concept to market
Leading role in pharma trials
--severe AD; Vascular Dementia; first gamma secretase modulator in mild-mod AD (phase 2);
--participated in Phase 1 and 2 MAB Trials

Major Stroke Centre with emphasis on Vascular Cognitive Impairment
--Co-led harmonization process for neuropsychological battery, currently being validated in NIH-funded study with U of Chicago, U of Hong Kong

Major Parkinson centre-- multi site U of T studies
--in pharmocogenetics of rivastigmine in Lewy Body Disease
--multimodal imaging study in Corticobasal Syndrome

Toronto alliance-- can increase size and scope of clinical trials for proof of concept of novel compounds
Frontotemporal Dementia Working Group involves all sites

--memantine study with glucose PET

--PPA study with imaging and comprehensive assessment of linguistic breakdown

--many studies on novel cognitive assessment methods, autobiographical memory, imaging-behavioural studies

--participating in consensus groups on criteria for bvFTD and PPA
U of Toronto-Dementia Research

Sunnybrook Dementia study

- longitudinal observational study ongoing for 15 years
- archive of > 1000 patients with neurodegenerative dementias, qMRI, SPECT, and detailed neurobehaviour

--- 100 publications, many by trainees structural imaging processing pipeline for efficient, individualized skull stripping and quantifying white matter disease

--- autopsies in 130 (eg have described clasmatodendrosis; and new progranulin mutations in collaboration with Rogaeva and St George Hyslop at CRND (Masellis et al Brain 2006))
Clinical Trials

- Targets
- Biomarkers
- Outcomes
- Co-morbidities
Targets

- Components of Pathological Cascades:
  - eg Amyloid, tau, progranulin, synuclein, stroke and occlusive arteriolar and venular cerebral small vessel disease
  - eg Mitochondria, lysosomes, misfolded proteins, free oxygen radicals, neurotransmitter systems
- Pure vs mixed disease syndromes
- Vascular risk factors
- Symptoms—cognitive—memory and executive functions, behavioural
Targets

- Disease stages-presymptomatic but high risk (FAD) Cognitive Impairment Not demented (MCI: amnestic, non-amnestic, multidomain); mild, moderate, severe stage disease
- Individuals, populations, people with common co-morbid brain diseases
- Alliance increases numbers allowing more study of subgroups, co-morbidities
Biomarkers

- Fluids: csf, blood
- Genes, proteins, lipids,
- Neuroimaging
  --Volumetric, Diffusion, Functional
  resting state/activated MRI, ASL
- Deoxyglucose and amyloid PET
Pittsburgh Compound B-PIB PET (Carbon 11)

Ng et al, J Nucl Med. 2007
Multimodal Outcomes

- Surrogates
  -- csf tau
  -- hippocampal/ whole brain volume changes/cortical thickness
  --- white matter disease
- Amyloid burden
- Functional Connectome—resting state control networks
Hippocampal Shape Change

Cognitive Outcomes

- Cognitive tool kit
  - MMSE, ADAS-Cog—undersample executive functions, which can be fractionated and behaviourally operationalized
  - VCI Harmonization battery (60-30-5min batteries)
  - Novel cognitive tools—autobiographical memory, strategy application, reaction time/attention battery,
  - ALS Battery with minimal motor output
  - BNA – Behavioural Neurology Assessment

- Cognitive Interventions
  - Goal Management Training

- Behaviour/Affective
  - NPI-Hallucinations (PET markers); Apathy
  - Neuropharmacology and Pharmaco-epidemiology studies (eg Lanctot and Herrmann et al)

- Quality of Life (Naglie et al)
Comorbid Brain Disease

- Vascular
- Lewy Body
- Multiple degenerative and vascular pathologies
In community autopsy series coexisting AD and CVD is common

In US population autopsy series:
- AD: 24-36%
- AD+CVD: 36-45%
- VaD: 3-13%

(Lim et al, JAGS, 1999; Snowdon et al, JAMA, 1997)

In a British population (median age 85):
- 70% had AD and 78% had CVD
- Small vessel disease was most common (69%) (Neuropath Group, Lancet, 2001)
Small Vessel Pathologies: Prevalence

- Leukoairiosis: 95% > 65 yrs
- Silent Stroke: 28% > 65 yrs
- Microbleeds: 30% of AD
Periventricular White Matter Disease as veno-occlusive disease

Courtesy of FQ Gao
New Approaches to clinical trials

Prevention in at risk populations
eg identified through genes or vascular risk factors using biomarkers (eg csf, amyloid labelling, qMRI)

Target--don’t ignore by exclusion- the majority of patients who have co-morbid disease such as AD/CVD
eg angiotensin blockers

Design proper instruments and obtain longitudinal imaging and behavioral data in the less common disorders such as Frontotemporal degeneration

Combine pharmacotherapy with cognitive and behavioural interventions (aerobic exercise)
Visualizing Plaques directly at 7T

Normal

Alzheimer patient

SWI MR Microscopy

Courtesy of Nakada et al AAN 2007