

Innovation Snapshot

Alzheimer's disease research in the Toronto Region

*"This is a time of extraordinary opportunity and innovation in ARD [age related dementias] research, spurred on by the new tools of health research: applied genomics and cheap, fast gene sequencing; real-time imaging of the functioning brain; nanotechnology and the potential for novel routes of drug delivery to the brain; and large, longitudinal population studies, supported by patient record databases and gene and tissue biobanks."*¹

- Canadian Institutes of Health Information

Introduction

First identified by Dr Alois Alzheimer in 1906, Alzheimer's disease is an irreversible degenerative brain disease characterized by symptoms which include cognitive impairment and the loss of ability to do simple tasks.²

Alzheimer's disease normally occurs over the age of 60 and represents 63% of all dementias, a term describing a set of symptoms caused by diseases which affect the brain. Other common causes of dementia include vascular dementia, Parkinson's Dementia and Lewy Body Dementia. People with dementia often exhibit problems with memory, thinking and speech, taking a large toll on family members and caregivers.³

Although the cause of Alzheimer's disease is not fully understood, scientific studies have shown that genetics

play a large role; having a direct relative diagnosed with Alzheimer's disease nearly triples a person's risk for developing the disease.⁴

According to a report commissioned by the Alzheimer Society of Canada, *Rising Tide: The Impact of Dementia on Canadian Society*, a little over 500,000 Canadians are living with Alzheimer's disease or other forms of dementia today. In 2008, the disease had an economic burden of \$15 billion annually. By 2038, the number of Canadians with Alzheimer's disease is expected to rise to 1.1 million at an annual cost of \$153 billion (Figure 1).³

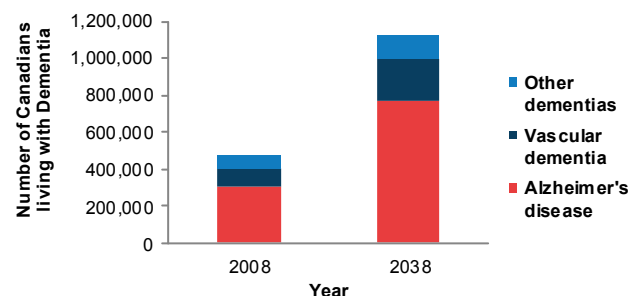
There are currently four approved drugs to temporarily alleviate symptoms of Alzheimer's disease. However, no treatment method exists to halt disease progression, nor are there accurate diagnostic methods. Post-mortem brain autopsies are considered the gold standard of diagnosis, but The 90+ Study examining people over age 90 has demonstrated that people without dementia may still exhibit physical hallmarks associated with Alzheimer's found via post-mortem autopsies.^{5,6} Therefore, conclusive diagnosis can often be difficult and drug development even more so.

With the anticipated social and economic burdens of Alzheimer's disease, there is a great urgency to find a solution. Toronto Region scientists and experts are pursuing innovative research in neuroimaging, genetics and assistive technology.

Did you know...

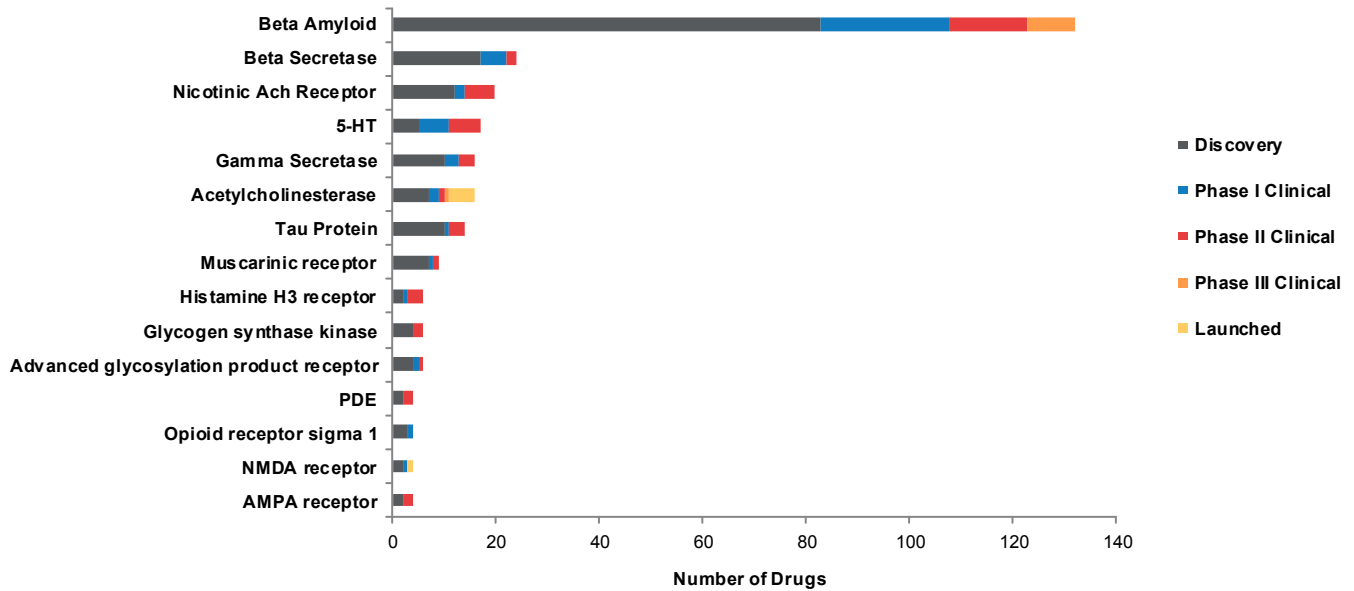
- In 2010, it was estimated that 36 million people worldwide had dementia
- Worldwide, dementia care had a economic burden of US\$ 604 billion in 2010

Figure 1: Prevalence of Dementia in Canada, 2008 and 2038



Source: Alzheimer Society of Canada

Figure 2: Top 15 Alzheimer's Disease Drug Targets



Source: TRRA analysis based on Thomson Reuters Pharma Data, 2011

Drug Targets

The majority of Alzheimer's disease drugs in development target beta amyloid, the main component of amyloid plaque which is a common feature of Alzheimer's disease. There are over five times as many drugs in development targeting beta amyloid than the second drug target, beta secretase (Figure 2).⁷ However, the drugs targeting beta amyloid are largely in discovery stage or Phase I clinical trials and none have been launched to date. Drugs that are in Phase III include Pfizer and Johnson & Johnson's drug bapineuzumab and Eli Lilly's drug solanezumab.

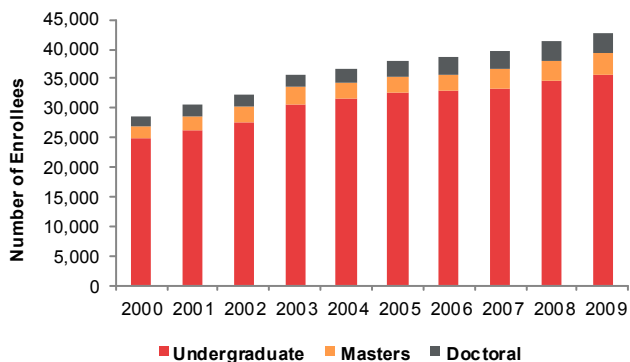
Four launched drugs for Alzheimer's disease target acetylcholinesterase and the NMDA receptor. These drugs only deal with symptoms and there are currently no drugs available to stop or slow the development of the disease.

Workforce & Education

In 2009, approximately 35,000 undergraduate and 7,000 graduate students enrolled in programs that could contribute to the research and development (R&D) of tests, treatments and devices for Alzheimer's disease (i.e. biochemistry, genetics, chemical engineering, electrical engineering) in universities across the Toronto Region (Figure 3).⁸

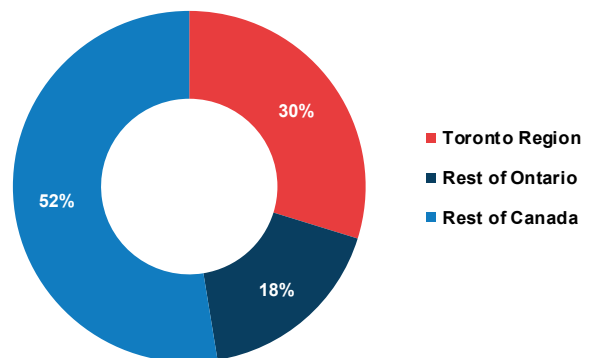
The Toronto Region also has an estimated 50,440 employees working in R&D related fields, such as chemists, chemical engineers and electrical engineers. The Toronto Region comprises 30% of the total related Canadian labour force (Figure 4).⁹

Figure 3: Number of Students Enrolled in Related Programs in Toronto Region Universities (2000-2009)



Source: TRRA analysis based on Council of Ontario Universities data

Figure 4: Regional Distribution of Related R&D Labour Force



Source: TRRA analysis based on Statistics Canada, 2006 Census

R&D Expertise in the Toronto Region

With many research-intensive institutes, university affiliated hospitals and sources of public sector funding, the Toronto Region presents a significant hub of Alzheimer's disease research.

Funding

The total captured public sector funding for Alzheimer's disease related projects in Canada was over C\$250 million between 2000-2010 from the various Canadian government funding committees. These include Natural Sciences and Engineering Research Council (NSERC),¹⁰ Canada Foundation for Innovation (CFI),¹¹ Canadian Institutes of Health Research (CIHR)¹² and Social Sciences and Humanities Research Council (SSHRC).¹³ In the Toronto Region, institutes received an estimated \$62 million, or 25% of nation-wide funding, with the University of Toronto receiving the most research funding of \$23 million over the last ten years (Figure 5). Other institutes such as Sunnybrook Research Institute and the Hospital for Sick Children also received substantial funding.

Over the past 10 years, the CIHR has allocated an increasing proportion of its total funding toward Alzheimer's disease research, signaling its growing importance. The compound annual growth rate (CAGR) over the 10-year period for Alzheimer's disease funding was estimated to be 16.1% compared to the total CIHR funding CAGR of 9.2%.¹²

Publications

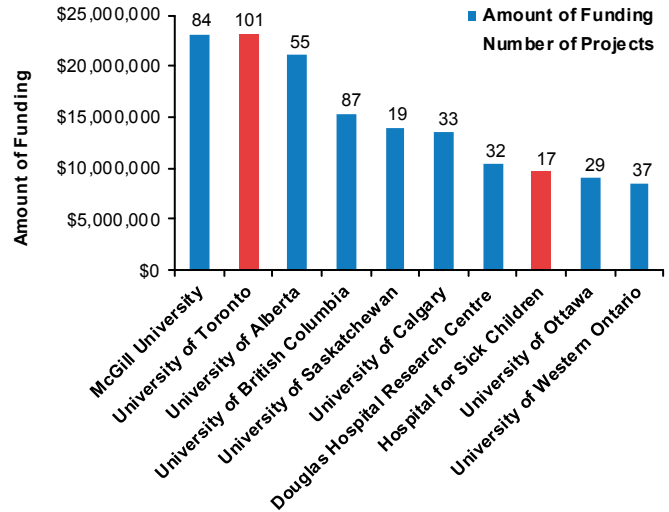
From 2000-2010, Canada ranked 5th in the world for both the number of Alzheimer's disease related citations and citation impact (Figure 6).¹⁴ Canada's average of 21.7 citations per publication is greater than the global average of 20.6 citations per publication. Globally, the University of Toronto ranked 10th for number of publications with 14,953 publications. Within Canada, the Toronto Region ranked 1st in number of Alzheimer's disease related publications, citations, and citation impact.

Patents

Canada ranked 6th globally by the number of Alzheimer's disease related patents. Within Canada, the Toronto Region ranked 2nd by number of patents (Figure 7).¹⁵ While most patents were assigned to global pharmaceutical companies such as Elan Pharmaceuticals and Pfizer, Canadian patent assignees were represented by a mix of companies and research institutes.

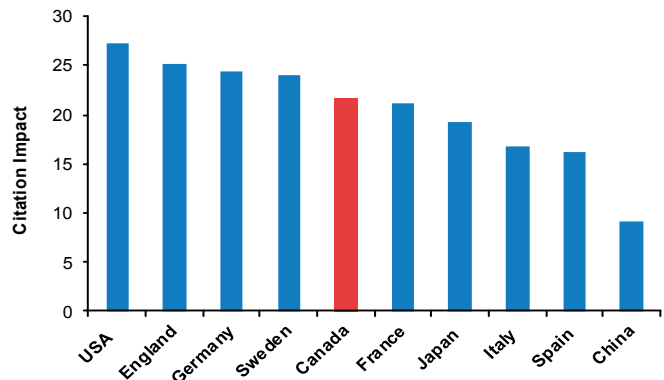
In the Toronto Region, the majority of patents were assigned to institutes such as the University of Toronto and the Hospital for Sick Children, demonstrating the strength of translational research originating from academic settings.

Figure 5: Top 10 Institutions in Canada by Amount of NSERC, CIHR, SSHRC and CFI Funding (2000-2010)



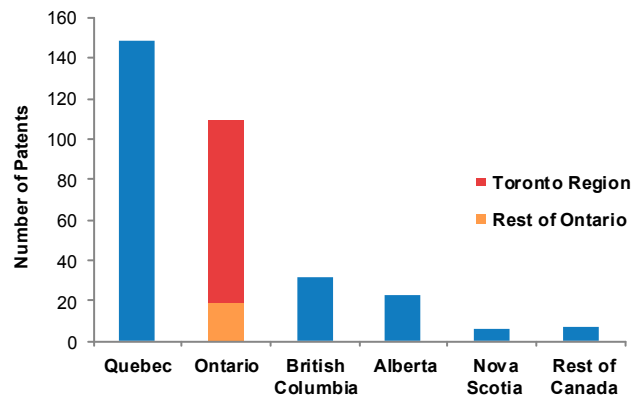
Source: NSERC, CIHR, SSHRC, CFI

Figure 6: Top 10 Countries by Citation Impact of Alzheimer's Disease Related Publications (2000-2010)



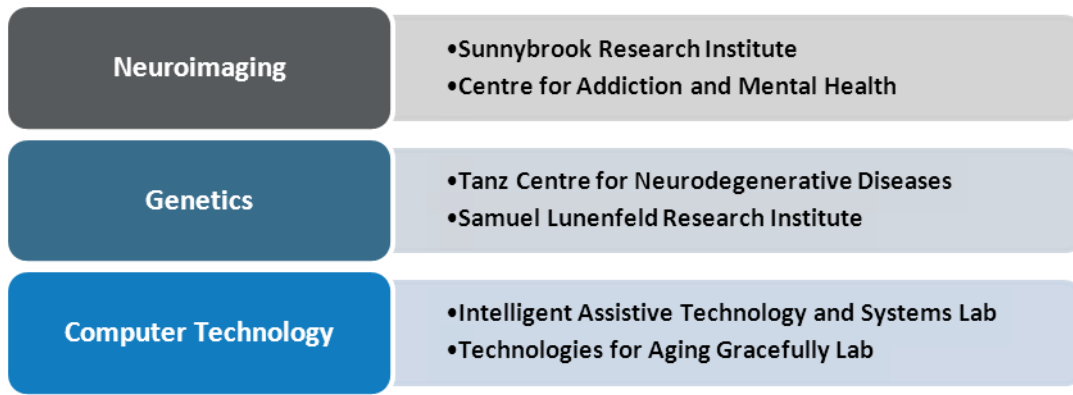
Source: ISI Web of Knowledge

Figure 7: Number of Alzheimer's Disease Related Patents in Canada (2000-2010)



Source: Delphion

Figure 8: Examples of Research Areas in Alzheimer's Disease and Related Research Institutes in the Toronto Region



Source: TRRA analysis

Institutes

It is no surprise that Toronto Region institutes generate a large portion of patents related to Alzheimer's disease. These institutes are actively conducting clinical trials and research relating to the diagnosis, treatment and neuroimaging of Alzheimer's disease (Figure 8). Below are a few notable institutes, their achievements and their ongoing projects:



- Baycrest's **Research Centre for Aging and the Brain** includes the Rotman Research Institute, one of the top five brain institutes in the world, and the Kunitz-Lunenfeld Applied and Evaluative Research Unit, which conducts translational neuroscience research.¹⁶
- This institute specializes in memory research and the effects of neurodegenerative diseases and the normal aging process.
- In 2008, Baycrest received \$10 million from private donations, matched by \$10 million from the Ontario government, to create the Centre for Brain Fitness. The centre aims to develop and market products which improve brain fitness.
- In 2010, a Baycrest study found that bilingualism delayed the onset of Alzheimer's symptoms.¹⁷



- The **Centre for Addiction and Mental Health** is the largest Canadian research facility focused on mental health and addiction.
- The facility is equipped with a position emission tomography (PET) facility and 13 PET radiotracers for human research.¹⁸

- Using a combination of genetic screening and imaging, a group at the institute is researching the effect of a variation of the BDNF (brain-derived neurotrophic factor) gene, val66met, on the brain and developing a method to identify pre-symptomatic Alzheimer's.¹⁹



- The **Intelligent Assistive Technology and Systems Lab (IATSL)** at the University of Toronto develops technology to assist people with dementia in their daily lives.²⁰
- The COACH project is designed to help people with dementia to remind them to do simple tasks such as hand washing. Clinical trials indicated that the program reduces caregiver reminders by 25%.



- A leading centre in biomedical research, the **Samuel Lunenfeld Research Institute** at Mount Sinai Hospital is conducting research focused on areas such as neurobiology, systems biology and cancer.²¹
- Researchers are developing a device for temporal manipulation of specific protein functions in the brain using laser optics techniques.



- **Sunnybrook Research Institute** is one of five Canadian institutes in the Alzheimer's Disease Neuroimaging Initiative (ADNI).^{22,23}
- The institute is actively conducting clinical trials and studies, and has an archive documenting over 1,000 patients with neurodegenerative dementia.²⁴

- The LC Campbell cognitive neurology group performs *in vivo* brain mapping to study relationships between Alzheimer's disease and cerebrovascular disease.
- Researchers in the Brain Repair Group, another research group at Sunnybrook, are also developing therapies that target beta amyloid and methods to regenerate neurons using progenitor cells.
- Other research areas include conducting trials for Memantine as a drug to help lessen behavioural and psychological symptoms of dementia and finding more accurate ways of diagnosing Alzheimer's disease.



- Established in 1990, the **Tanz Centre for Research in Neurodegenerative Diseases** (CRND) specializes in neurodegenerative disease research such as Parkinson's Disease, Alzheimer's disease and Frontotemporal dementia.²⁵
- Contribution to the identification of apolipoprotein e 4 gene as a risk factor in 1993.
- Patent application for TgCRND8, a mouse model for early-onset Alzheimer's, used in studies to identify early indicators of the disease, in 2001.²⁶
- Contribution to the identification of another four genes linked to late-onset Alzheimer's disease in 2011.²⁷



- The **Technologies for Aging Gracefully Lab** at the University of Toronto focuses on developing technologies to assist older people with projects that help improve cognition and communication.²⁸
- "Digital Life Histories" is one such project, where researchers are testing the use of a Microsoft-developed camera capable of taking pictures automatically and delivering narratives. Researchers intend to use the "SenseCam" to engage people with Alzheimer's disease to help them recall events and also to promote social interaction.
- Another project in the works is an on-line mental fitness platform called Tangra, which aims to study the effectiveness of several mental fitness games or activities and assist researchers in developing further programs.

Collaborations Around The World

Recently, several collaborations have been formed to help accelerate advances and to encourage the exchange of research data. The effectiveness of such collaborations was demonstrated recently in the identification of several genes linked to late-onset Alzheimer's disease. The following are two collaborations between institutes in North America:



The **Alzheimer's Disease Neuroimaging Initiative** (ADNI) is the largest public-private partnership in Alzheimer's disease research to date, with 54 institutes from USA and five from Canada collaborating to share findings and clinical trial results. Led and mostly funded by the National Institute of Aging (USA), funding also comes from pharmaceutical companies such as GlaxoSmithKline and Bristol-Myers Squibb. The project has received US\$ 60 million in funding.²²

Launched in 2004, the overall goal of this initiative is to develop better methods for conducting clinical trials, to track the progression of Alzheimer's disease by using imaging devices and also to determine who is at risk. The project has expanded to new phases, ADNI GO and ADNI2. Sunnybrook Research Institute, one of the few Canadian contributors to the project, is currently enrolling volunteers to participate in these studies.



Led by University of Pennsylvania's School of Medicine, the **Alzheimer's Disease Genetics Consortium** is investigating genes linked with late-onset Alzheimer's disease and is funded by a five-year National Institute of Aging grant of US \$18.3 million dollars.²⁹

The Alzheimer's Disease Genetics Consortium Study together with another research group from Europe, The Genetic and Environmental Risk in Alzheimer's Disease group, were responsible for the identification of four additional genes linked with late-onset Alzheimer's disease. The study involved the collaboration between 44 institutes (including the University of Toronto) and the genetic evaluation of over 11,000 people with Alzheimer's disease.^{27,30}

Dr Peter St George-Hyslop from the Tanz CRND at the University of Toronto is currently on the executive committee. (See Experts Section, p. 6.)

Experts

The Toronto Region is home to 15 Canada Research Chairs (CRC) in the area of Alzheimer's disease (Figure 9).³¹ The following are the top publishing experts in the Toronto Region:



Dr Sandra Black

*Director, LC Campbell Neurology Research Unit
Senior Scientist, Sunnybrook Research Institute
Brill Chair of Neurology, University of Toronto*

Dr Black's research focuses on using neuroimaging to diagnose and monitor several neurodegenerative diseases such as Alzheimer's disease and other dementias. She has a particular interest in vascular causes of dementia and interactions of Alzheimer's and cerebrovascular disease. Dr Sandra Black has over 300 publications, including 113 articles on Alzheimer's disease, and is active as a Principal Investigator on a number of clinical trials relating to dementia.³²



Dr Gabrielle Bouilanne

*Tier 1 Canada Research Chair in Molecular & Developmental Neurobiology
Senior Scientist, Hospital for Sick Children
Professor, University of Toronto*

Dr Bouilanne's research involves the identification of genes associated with Alzheimer's disease and aging, using the common fruit fly as a model for Alzheimer's disease. Funded by the Canadian Institutes of Health Research, her research aims to elucidate novel risk factors and identify new therapeutic targets for Alzheimer's disease.³¹



Dr Peter St George-Hyslop

*Director, Centre for Research in Neurodegenerative Diseases
Director, Memory Disorders Clinic
Professor, University of Toronto*

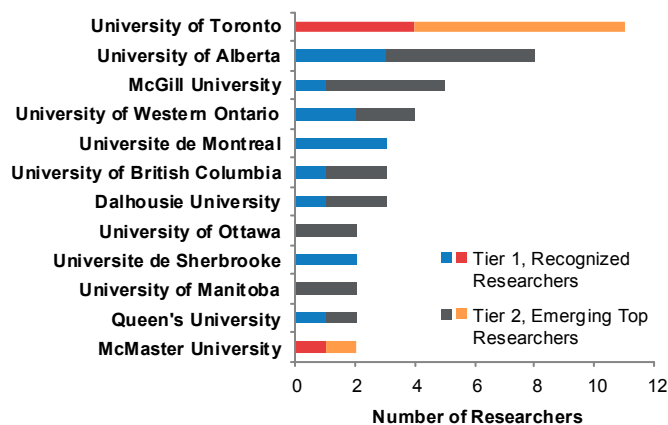
A renowned neurologist who has won multiple awards for his work relating to Alzheimer's disease, Dr St George-Hyslop's research interests include the study of genes associated with human neurodegenerative diseases with a main focus on Alzheimer's disease. His contributions to the field include the identification of apolipoprotein e 4 (apoE4) as a risk for Alzheimer's disease and also the defective gene Presenilin1 whose mutation is the most common cause of familial early-onset Alzheimer's disease. Dr St George-Hyslop also leads a team at the Tanz CRND that helped identify four new genes linked to late-onset Alzheimer's disease.^{25,27}

Clinical Trials

Many institutes and research hospitals in the Toronto Region are active in conducting clinical trials for Alzheimer's disease drugs in development. Over the past seven years, there have been at least 65 clinical trials mainly taking place in hospitals such as Sunnybrook Health Sciences Centre in Toronto and St Peter's Hospital in Hamilton (Figure 10).³³ Overall, more than half of the trials are industry-funded.

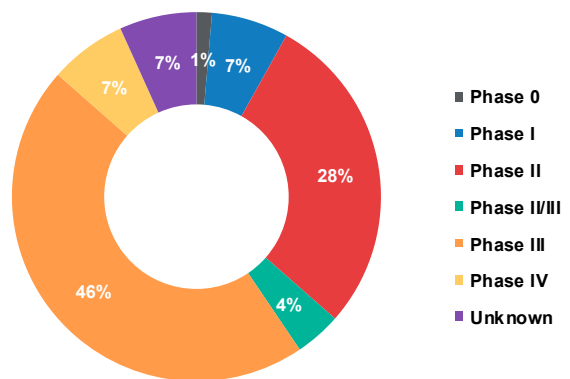
Clinical trials taking place in the Toronto Region include the industry-funded Phase II trial by Novartis to develop a vaccine which targets beta amyloid protein.³³ Physician-funded trials involving neuroimaging are also taking place with ADNI GO and ADNI 2, where investigators are measuring the progression of Alzheimer's disease. The Toronto Memory Program is a centre active in conducting trials, and has been involved in over 50 trials relating to Alzheimer's disease.³⁴

Figure 9: Alzheimer's Disease Related Canada Research Chairs by Institution and Tier



Source: TRRA analysis based on CRC data, 2011

Figure 10: Stages of Clinical Trials in Ontario



Source: TRRA analysis based on ClinicalTrials.gov data, 2011

Companies



Transition Therapeutics (Toronto)

Transition Therapeutics is a biopharmaceutical company which researches and performs clinical trials on drugs used to treat diseases such as Alzheimer's disease and diabetes.³⁵ Their current focus is ELND005, an orally-administered treatment for Alzheimer's disease. With the completion of Phase II clinical trials in 2010, the company plans to advance ELND005 to Phase III in partnership with Elan Corporation, a neuroscience-based company.



Amorfix Life Sciences Ltd (Mississauga)

Amorfix is a biotechnology company that develops diagnostic tests and therapeutics for diseases such as Alzheimer's disease and amyotrophic lateral sclerosis.³⁶ The company has developed a post-mortem diagnostic test for beta amyloid, a common feature of Alzheimer's disease in the brain, in animal models. The Amorfix Aggregated A β Assay detects beta amyloid plaques without formic acid extraction, which eases the detection process and is also capable of detecting beta amyloid peptides prior to the development of plaques faster than immunohistochemistry methods. Amorfix is currently developing a human diagnostic assay to detect aggregated beta amyloid from cerebral spinal fluid and blood. Amorfix is also collaborating with University of British Columbia scientists to develop Alzheimer's disease treatments.

Functional Neuromodulation Inc. (Toronto)

Founded in 2010, Functional Neuromodulation Inc. is a Toronto-based medical technology company that is developing treatment methods of Alzheimer's disease and Mild Cognitive Impairment by using Deep Brain Stimulation (DBS).³⁷ This technology involves the placement of pacemaker-linked electrodes in the brain. The company was co-founded by Dr Andres Lozano, a Tier 1 Canada research chair in neuroscience, who recently completed Phase I clinical trials using Deep Brain Stimulation on six patients with mild Alzheimer's disease. These preliminary studies showed that the therapy was safe and could potentially slow the progression of Alzheimer's disease. This technology has already been used to help patients manage Parkinson's Disease and researchers are currently looking at other applications of Deep Brain Stimulation which include treating major depression and epilepsy.³⁸

Did you know...

- In Canada, Alzheimer's disease was the 7th leading cause of death in 2007⁴²
- In the same year, women accounted for seven out of 10 deaths due to Alzheimer's disease⁴²

Conclusion

An increasing number of people will become at risk of developing Alzheimer's disease as Canada's population ages; 25% of the Canadian population will be over the age of 65 by 2031. With these statistics, the importance of Alzheimer's disease research and continuing advances is clear.

The following are a few recent Canadian initiatives to enhance research and development activities in Canada:

- The Canadian federal government recently allocated \$8.6 million for 44 Alzheimer's disease research projects³⁹
- The **Ontario Brain Institute** will receive \$15 million from the province over a three-year period⁴⁰
- **Canadian Dementia Knowledge Translation Network** established in 2008, encourages the exchange of research information between scientists and helps researchers apply their scientific research knowledge in useful services and treatments⁴¹
- Canadian Institutes of Health Research's funded strategies/projects: **The International Collaborative Research Strategy for Alzheimer's disease** and the **Canadian Longitudinal Study on Aging**¹

With renowned experts, well-equipped research facilities, a continuous supply of research talent and the support of government funding, the Toronto Region is an attractive and vibrant location that offers great opportunities to be at the forefront of advancements in the field of Alzheimer's disease research.

TRRA would like to acknowledge Dr Jack Diamond, Scientific Director of Alzheimer Society of Canada, for sharing his insights into cutting-edge knowledge in Alzheimer's disease research.

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