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## THE GLOBE AND MAIL

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# Dementia researchers feel blocked by Ottawa, big pharma, medical dogma

By Carolyn Abraham  
From Saturday's Globe and Mail

*Drug companies' hopes for a cure are dashed. Ottawa has been slow to listen. Now leading scientists are taking action*

Last year, in a flurry of calls and e-mails, Canada's leading Alzheimer's researchers quietly hatched a plan to fight a war on two fronts - scientific and political.

In their field, failures were piling up. Drug after drug had flopped in trial after trial - five in the previous two years alone. Pharmaceutical giants and boutique biotechs had spent hundreds of millions chasing therapies that have turned out to be useless, toxic or both. And every dud cast fresh doubt on the basic biology of the disease.

"It's been far more complicated at every step of the way than anyone thought," says Peter St George-Hyslop, director of the Centre for Research in Neurodegenerative Diseases at the University of Toronto.

With nothing to cure or even slow it down, Alzheimer's is poised to become one of the great public-health burdens of the 21st century. The few drugs available offer no more than the fleeting relief of symptoms that steal the mind.

"No one thought 10 years ago we'd be this far behind," says Howard Chertkow, a cognitive neurologist at McGill University and director of the Bloomfield Centre for Research in Aging at the Jewish General Hospital.

Politically, meanwhile, finding funding to help solve the mystery has proved nearly as challenging as the disease. "As a problem of aging, Alzheimer's is not that sexy," Dr. St George-Hyslop says. It's not "hot like breast cancer or HIV" and lobbying efforts suffer when "affected people cannot speak for themselves."

So last year the researchers decided to speak with one voice, by forming the Canadian Dementia Action Network (CDAN) - a plucky band of white coats ready to leave the lab and press the government to fund their urgent, daunting hunt for treatments.

"We don't really understand the intrinsic, basic mechanisms involved" in Alzheimer's - Jean-Marie Leclerc, a vice-president and chief scientific officer of Novartis Canada

Yet despite 39 letters of support from international politicians and researchers, Ottawa has not been convinced. Neuropathologist Patrick McGeer says that federal Health Minister Leona Aglukkaq "has refused even to discuss it with us."

Although work has begun slowly on a national approach, Dr. Chertkow notes, "Canada at the present time is the only technologically advanced country with no national strategy on how to fight and cure Alzheimer's disease."

### **Profits versus patients**

Some observers blame the inertia mainly on the course of Alzheimer's research itself, which for decades has focused single-mindedly on a hypothesis now in doubt.

Others say that with no foolproof way to diagnose Alzheimer's early, before symptoms set in, there simply has been no way to properly test any treatment that might reverse it.

A few fault the profit motives of the pharmaceutical industry. One of them is Dr. McGeer, a professor emeritus at the University of British Columbia who has been one of the most published Alzheimer's researchers over the past 40 years and is still active.

"The failure of getting something effective to the bedside is because of the schism between basic science and commercial interests," he says.

The common pain reliever ibuprofen, for example, may reduce the risk of Alzheimer's. But, says Dr. McGeer, companies haven't tried it because they are interested only in compounds they can patent.

"The result has been an unbroken string of disappointments in pharmaceutical- company-sponsored clinical trials ... and nearly all could easily have been predicted to end in failure. Clinicians are stuck."

At least nine drug trials have ended abruptly since 2005, several in advanced stages of development and some of them run by the biggest names in pharma, including Pfizer Inc., Merck and GlaxoSmithKline. Most recently, Eli Lilly halted a late-phase trial in August after finding that its drug made some patients worse.



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Yet trials begin "in good faith," insists Jean-Marie Leclerc, a vice-president and chief scientific officer of Novartis Canada, speaking as the medical-committee chair at Rx&D, which represents 50 pharmaceutical companies across the country. Drug makers can spend roughly \$800-million getting a treatment to a phase 3 trial. "Nobody plans for failure."

At least 90 per cent of drug candidates for any disease never make it to market, Dr. Leclerc adds. The failures, he says, are "very frustrating for all of us," but there is something to learn from them: "We don't really understand the intrinsic, basic mechanisms involved" in Alzheimer's.

When Dr. McGeer first contacted colleagues to suggest they put aside any competitive interests to collaborate and test treatments the drug industry might not, it didn't take much convincing. Even researchers who do not share his criticisms of the drug industry could see the urgent need to combine the sum of their parts and overcome the "scattered" nature of projects.

CDAN has since formed nine national teams to investigate new treatments at all stages - from cells in a dish, to animal models, to patients. Academic groups with similar aims have sprung up in Europe and the U.S.

Dr. Chertkow, who heads the Canadian group's clinical-research team, hopes that the group will drive investigations in new directions: "It has been very hard for brilliant scientists in Canada to push hard for unconventional ideas that deserved serious study. Between inertia and conservatism in pharma, and the same in the funding agencies ... things have moved forward at a snail's pace."

As well, he notes, "for 15 years the amyloid [hypothesis] has taken such centre stage that other things have not been studied or funded in the way that they should."

That hypothesis dates back more than 100 years, to the death of Auguste D., a German woman who at the age of 50 had forgotten how to write her name, spent nights screaming, dragged bed sheets through the house and slipped into vegetative states.

Her husband dropped her off in 1901 at a Frankfurt asylum, where she told neuropathologist Alois Alzheimer, "I've lost myself."

After her death in 1906, Dr. Alzheimer gave a landmark lecture describing the posthumous state of her brain - thin cortex, covered with plaques and nerve fibres tangled like spaghetti.

"One perspective has held court for 30 years - it's nuts. What science does that? All these people, all this money, and we still don't have an answer" - Suzanne DeLaMonte, a neuropathologist at Brown University

Some experts suspect the tangles, formed by a protein called tau, are central to the disease. But it was the amyloid plaques that emerged as the key culprit in the 1980s. Researchers discovered that a genetic mutation that results in build-ups of amyloid - part of a protein that the healthy brain clears away - is associated with Alzheimer's in people as young as 40.

The hypothesis suggests that sticky bits of this protein fragment accumulate and clump into plaques that trigger Alzheimer's disease - leading to tangles, and cell death.

But in the three decades that it has dominated research, the theory has taken serious blows. Autopsies and brain scans show many people with plaques don't have Alzheimer's or dementia. Some experts suspect those people will develop disease eventually if they live long enough, but no one knows with certainty.

"Do the plaques and tangles cause Alzheimer's? Are they a symptom of the disease? The literature is a mess," says Suzanne DeLaMonte, a neuropathologist at Brown University in Rhode Island. "But there has been so much investment of researchers and pharmaceutical companies, they don't want to let this go.

"One perspective has held court for 30 years - it's nuts. What science does that? All these people, all this money, and we still don't have an answer."

At the same time, drug candidates designed to fight amyloid have shown no benefit. A 2008 British trial with 64 patients, for instance, found that a vaccine that did clear away plaques did nothing to prolong survival or improve their dementia.

"It's too early to say the amyloid hypothesis is dead, but each time an amyloid treatment fails, the hypothesis looks a little weaker than it did before," McGill's Dr. Chertkow says. Some recent research suggests the plaques may

even play a protective role in the brain.

## Chasing ghosts

In April, an independent panel of experts convened by the U.S. National Institutes of Health reviewed the state of Alzheimer's research and reached a bleak conclusion: No one knows what causes the disease and no reliable evidence exists to suggest that anything - not vitamin pills nor crossword puzzles - prevents it.

Treating any brain disease is tricky, Dr. St George-Hyslop says. "The brain is the most complex organ in the human body."

He and other experts suspect current trials may be doomed because they involve patients with symptoms and brain damage too far along for any drug to fix. "It may be that, if you give amyloid treatments 10 years before symptoms appear, maybe you can make a difference."

This is why brain scans and the recent discovery of biological markers to predict who may develop Alzheimer's could allow drug trials at an earlier stage, he says.

But testing a treatment in someone only predicted to have Alzheimer's also presents a classic, agonizing Catch-22.

"You have to hope your biomarkers are as good as you think they are, and then you have to wait years to see if the treatment will have any effect - and the fact is, that person might not have Alzheimer's disease anyway," Dr. St George-Hyslop says.

In that case, there is no way to say a treatment actually did anything. (At present, Alzheimer's can be diagnosed definitively only in an autopsy.)

However, as the leader of the new network's genetics team, Dr. St George-Hyslop still feels that "there has been brilliant progress" in understanding Alzheimer's at the molecular level. The field "is on the cusp" of realizing it is not one disease, but several subtly different forms of neurodegeneration with common features, he says. Much like cancer, these may require not just one drug, but several.

## Plan versus plan

In March, Dr. McGeer (who served in the B.C. legislature from 1962 to 1986) presented the CDAN network's own plan to the federal government. He had high hopes, since a similar group he launched in B.C. in 2004 had received \$15-million from the province. But Ottawa has not even agreed to a meeting, he says.

When asked about this stalemate this week, the federal Health Minister's office replied by e-mail, saying that Alzheimer's and dementia research is a priority for the government, but falls under the purview of the Canadian Institutes of Health Research, the main federal funding body for medical research.

Remi Quirion, an Alzheimer's researcher and vice-dean at McGill who is the former director of the Institute of Neurosciences at CIHR, says he was asked a year ago to develop an International Collaborative Research Strategy for Alzheimer's Disease. It focuses heavily on prevention, early diagnosis and teaming Canadian scientists with groups in other countries.

The CIHR has set aside \$5-million in each of the next five years out of its budget to put that plan in motion, but Dr. Quirion agrees that funding should increase: "We need about 10 times that amount."

For its part, CDAN has asked for exactly that - \$50-million in each of the next five years - to fund its plan. Unlike the CIHR's, it would not require researchers to compete for grants in a way that could make progress halting.

But Dr. Quirion says that while CDAN has laudable goals, it should come under the CIHR umbrella, so as not to duplicate efforts or "create a whole new bureaucracy." He hopes to meet with CDAN researchers in October in hopes of taking a "unified plan" to Ottawa and the provinces, asking for dedicated funding of about \$250-million

spread over five years, which he says matches the amounts other countries spend on dementia research.

For Dr. McGeer, the matter comes down to simple calculations: "We spend \$18-billion a year in Canada to look after people with dementia. That's \$50-million a day," he says.

"We are asking for less than the equivalent of two fighter jets - and we think Canada can make a better contribution to the world by finding a truly effective treatment for Alzheimer's disease."

*Carolyn Abraham is the Globe and Mail's medical reporter.*

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