

Review

Targeting Alzheimer's Disease at the Right Time and the Right Place: Validation of a Personalized Approach to Diagnosis and Treatment

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Abstract. Cautious optimism is appropriate for a near future (five years) time frame for a number of drugs acting on the different pathophysiological components of Alzheimer's disease (amyloid deposition, tau hyperphosphorylation, neuroinflammation, vascular changes, to name the most important known so far). Since the relative weight of these components will be different between individuals and will even change over time for each individual, a 'one drug fit for all' approach is no longer defensible. Precision medicine using biomarkers in the diagnosis and treatment of Alzheimer's disease is the new strategy.

Keywords: Alzheimer's disease, biomarkers, brain imaging, database analysis, diagnosis, human volunteer cohorts, precision medicine, translational research, treatment

MISE-EN-CONTEXTE

The traditional treatment approach: Monotherapy for all patients with the Alzheimer's disease phenotype

The renaissance of interest for Alzheimer's disease (AD) started in the 1970s when a cholinergic deficit was discovered, leading to a transmitter-replacement therapy using cholinesterase inhibitors. A modest but clinically meaningful improvement was demonstrated in randomized clinical trials (RCTs) and in

clinical practice for mild to severe stages of dementia. The NMDA-receptor antagonist memantine was then found to improve patients in moderate to severe stages of dementia. Proof of additive benefit from the two classes of drugs is still equivocal. These drugs proved to be relatively safe considering the age and co-morbidity of most users [1].

The next phase of AD research centered on amyloid- β ($A\beta$)₄₂, in late onset sporadic as well as early familial AD. At the dementia stage of AD, no RCTs targeting amyloid have been successful to this date, despite multiple attempts using active or passive immunization, BACE-inhibitors, and γ -secretase inhibitors, in patients known to have amyloid pathology using positron emission tomography (PET) scanning or cerebrospinal fluid (CSF)

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examination. The most encouraging study is a Phase Ib RCT using aducanumab in mild AD which showed a dose-related reduction in amyloid load using PET as well as clinical stability [2].

A first attempt at treating the tau pathology associated with AD using an orally administered tau aggregation inhibitor led to equivocal results in mild to moderate dementia [3]. Other studies are being initiated using monoclonal antibodies [4]. Tau pathology is now recognized as a key driver of disease progression in AD, and strategies are being developed to accelerate drug development from animal models, such as antibodies against the proximal N-terminal domain tau 6–18 in 3XTg-AD mice [5], to human RCTs [6].

Finally, attempts at reducing the levels of neuroinflammation using non-steroidal anti-inflammatory drugs such as naproxen have failed to modify cognitive decline in persons at risk or with dementia due to AD [7].

New diagnostic criteria using biomarkers

The clinical progression of AD is linked to specific neuropathological features, such as extracellular deposition of A β plaques, intracellular inclusions of tau protein in neurofibrillary tangles, and neuronal degeneration. The discovery and advance of disease biomarkers over the last decade have significantly advanced our understanding of the dynamic pathophysiological changes underlying AD and have allowed the detection of AD pathophysiology *in vivo* [8]. Given that the presence of AD pathophysiology has been found across a broad clinical spectrum including individuals asymptomatic and with mild cognitive symptoms, biomarkers now play an important role in characterizing the trajectory of AD pathophysiology and have been incorporated in the AD diagnostic research criteria [9–12]. These diagnostic research criterions recognize that the coexistence of abnormal A β and tau biomarkers better identify the preclinical and mild cognitive impairment (MCI) individuals who will progress to dementia over relatively short time frames of three to five years. These concepts also apply to well to early onset familial AD [13].

Such advances in understanding the natural history of AD have been made possible through concerted international efforts at pooling the database of research cohorts. Indeed, analysis of the data obtained from cohorts of volunteers undergoing periodic clinical, neuropsychological, and biomarkers

assessments have led to multiple publications, which further enhance our knowledge of the AD process. The Alzheimer's Disease Neuroimaging Initiative (ADNI) is the best known of these cohorts, and the open access of these data to scientists is considered as a model for science as a whole. Access to the Dominantly Inherited Alzheimer Network (DIAN) database is more restrictive because of specific ethical considerations due to the genetic status of the participants.

The identification of AD biomarkers crossing pathological threshold in cognitively normal individuals has led to the conceptual framework of a preclinical stage in AD [14]. This operational definition of preclinical AD has made possible ongoing RCTs in individuals by the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) [15] and the Anti-Amyloid treatment in Asymptomatic AD (A4) study [16], given that early intervention may offer the greatest chance of treatment success.

New concept of individualizing the underlying pathophysiological components of AD

Based on histopathological and genetic evidence, fibrillar A β , the main constituent of A β plaques, has been postulated as the major driving force leading to AD dementia (amyloid cascade hypothesis). According to this hypothesis, all the resulting pathological processes are due to an imbalance between A β production and clearance, which would then potentiate the spread of tauopathy, leading to neurodegeneration and cognitive decline. However, the lack of consistent association between A β and clinical progression, and the fact that amyloid pathology has been found in cognitively normal elderly individuals challenge the A β hypothesis in its original form. For example, tau pathology has been reported in the brains of non-demented subjects in the transentorhinal, limbic, and basal temporal regions [17, 18], while studies have shown that either A β or neurodegeneration may be the first biomarker abnormality in preclinical AD [19]. Therefore, alternative pathways of the AD pathophysiology independent of A β have been suggested [20, 21].

An unbiased biomarker classification system, A/T/N, which avoids the assumptions of the temporal ordering of AD biomarkers, has been proposed [22]. In this classification system where each biomarker category is binarized as either positive or negative, "A" represents A β biomarkers using amyloid PET or CSF A β_{42} , "T" represents tau biomarkers

using CSF p-tau or tau PET, and “N” represents neurodegeneration biomarkers using CSF p-tau, structural magnetic resonance imaging (MRI), or [^{18}F]fluorodeoxyglucose PET (FDG). This descriptive classification aims to organize the multi-modality biomarker results at the individual person level in a way that is easy to adopt and interpret. Other brain pathological processes have been postulated as natural candidates to integrate this unbiased system. Studies under way are measuring simultaneously the amyloid, tau, and neuroinflammation in individuals, with follow-up over time to test the hypothesis that the coexistence of the brain pathological factors may accelerate AD clinical manifestations (*vide infra*). If confirmed, the A/T/N classification of individuals may be broadened to A/T/N/NI, where “NI” represents neuroinflammation biomarkers. Another important biomarker candidate is the presence of concomitant cerebrovascular disease. Indeed, results from DIAN cohort have already suggested white matter hyperintensities as a core pathological feature of autosomal AD [23], and a multifactorial causal model analysis using ADNI demonstrated the importance of vascular dysregulation as an important initial pathologic event leading to late onset AD [24].

CONTRIBUTIONS OF THE MCGILL CENTER FOR STUDIES IN AGING TO THE FIELD

Our main research activities over the past three years are summarized in Table 1.

Translational research from animal models, human postmortem tissues, and in vivo human volunteers

One of our research strategies has been a translational approach to the study of cerebral biomarker changes with age and in AD participants, as well as animal models. For example, using the McGill-R-Thy1-APP rat model, we were able to simultaneously demonstrate changes in MRI, CSF, PET, and brain tissue levels of $\text{A}\beta_{42}$ over time [25, 26]. The less aggressive $\text{A}\beta$ progression in these transgenic rats makes this model more similar to the insidious progression of late onset human sporadic AD. Also, the relatively large brain size of these rats makes possible the identification of specific brain structures using PET. It is important to mention that, using a CSF cisternal collection technique, we were able to perform the first longitudinal study of CSF at multiple

time points *in vivo* without causing any harm to the animals. Additionally, one of our interests is to bridge the knowledge from these studies in animals to human volunteers. In this regard, over the past few years, we have also been able to bridge studies in animal models [27] and human volunteers for cholinergic denervation [28], and similarly for glutamate mGluR5 receptors studies [29]. We also have successfully begun working with PET radiotracers demonstrating tau binding with high specificity relative to monoamine oxidase [30], and we have proven that [^{18}F]FDG depicts astrocytic activity in addition to synaptic neuronal activity [31].

Prospective study of age-associated biomarkers

Cortical thickness using MRI has been studied in a cohort of cognitively normal (CN) persons between ages of 40 and 80, at two-year intervals. In this cohort, we have genetically and morphologically characterized familiarity deficits as an early cognitive marker for individuals at risk for AD [32, 33].

We are currently simultaneously studying over time amyloid, tau, and neuroinflammation using PET imaging. This new cohort includes cognitively normal older persons, MCI due to AD, and mild dementia due to AD in early onset familial cases as well as late onset sporadic cases, as a first step to a personalized approach to treatment targeting multiple pathological pathways (*vide infra*).

Research using large database

Another successful approach has been the study of the interaction between $\text{A}\beta_{42}$ and tau biomarkers in AD, using the ADNI database. We found that the synergy of $\text{A}\beta$ and hyperphosphorylated tau, rather than their individual effects, drives metabolic decline in preclinical AD (Fig. 1) [34], and that this synergy also predicts progression from MCI to dementia [35]. Other uses of ADNI include linking immune cascades and cerebral amyloidosis using epistasis analysis [36], finding biomarker characteristics of rapidly progressive AD [37] and of CN individuals with ventriculomegaly [38], and a correlation between early neuropsychiatric symptoms and hypometabolism in preclinical AD [39].

Another important database for our analysis is DIAN. A first study looking at suicidality risk in carriers and non-carriers suggests a similar risk, and a prediction model using neuropsychiatric symptoms and neuroimaging/CSF biomarkers is under study.

Table 1
Main research activities in the MCSA over the past three years

Study subjects (Sample size)	Study design	Biomarkers	Main outcome measured	Scientific Contribution	Reference
<i>Translational research from animal models, human post-mortem tissues and in vivo human volunteers</i>					
5 bvFTD 10 CN	Case-control	[¹¹ C]ABP688 PET	Glutamatergic abnormalities	First <i>in vivo</i> report of decreased availability of mGluR5 in FTD.	[29]
11 wild-type rats	Drug challenge	[¹¹ C]ABP688 PET	Glutamatergic binding sites	Supports that mGluR5 availability is sensitive to extracellular glutamate.	[54]
5 CN 7AD	Case-control	[¹⁸ F]FEOBV PET	Cholinergic denervation	First quantification of brain cholinergic denervation in AD patients.	[28]
5 MCI 2 AD 1 PSP	Drug challenge	[¹⁸ F]THK5351 PET	MAO-B availability	First <i>in vivo</i> study showing that [¹⁸ F]THK5351 highly depict MAO-B availability, rather than tau deposition, in the brain.	[30]
13 wild-type, 13 McGill-R- Thy1-APP	Longitudinal observational cohort	[¹⁸ F]Florbetapir and [¹⁸ F]FDG PET. CSF A β and tau. MRI.	Biomarkers change over time	Suggests that A β itself is sufficient to impose focal memory circuits dysfunction	[26]
10 wild-type rats	Drug challenge	[¹⁸ F]FDG PET	[¹⁸ F]FDG availability	First study showing strong evidence that astrocytes contribute significantly to the [¹⁸ F]FDG signal.	[31]
<i>Research using large database</i>					
196 CN 324 MCI 70 AD	Epistasis analysis	[¹⁸ F]Florbetapir PET. CSF A β and tau.	Fibrillary amyloid- β	Genetic components linking the immune system and brain amyloidosis.	[36]
120 CN	Prospective longitudinal observation	[¹⁸ F]Florbetapir and [¹⁸ F]FDG PET. CSF A β and tau.	Changes in glucose metabolism	First study showing the synergy between A β and tau drives metabolic decline in preclinical AD	[34]
314 MCI	Case-control	[¹⁸ F]Florbetapir and [¹⁸ F]FDG PET. CSF A β and tau.	Progression to dementia	First study showing that a synergy between A β and tau determines the progression to dementia	[35]
312 mild AD	Prospective longitudinal observation	[¹⁸ F]Florbetapir and [¹⁸ F]FDG PET. CSF A β and tau. MRI.	Rapid progression to dementia	Identification of the biomarkers best associated with rapid progression to dementia	[37]
115 CN	Prospective longitudinal observation	[¹⁸ F]Florbetapir and [¹⁸ F]FDG PET. CSF tau. Neuropsychiatric symptoms	Changes in glucose metabolism	Supports that neuropsychiatric symptoms constitute an early clinical manifestation of AD.	[39]
425 CN	Prospective longitudinal observation	[¹⁸ F]Florbetapir and [¹⁸ F]FDG PET. CSF A β and tau. MRI (ventriculomegaly)	Biomarkers change over time	Ventriculomegaly might be an early imaging signature of AD and/or normal pressure hydrocephalus.	[38]
<i>Prospective study of age-associated biomarkers</i>					
81 CN	Prospective longitudinal observation	APOE ϵ 4	Familiarity performance	APOE ϵ 4 is associated with a reduction in familiarity in the absence of other cognitive deficits.	[32]
81 CN	Prospective longitudinal observation	Structural MRI	Familiarity performance	Familiarity is associated with the cortical volumes in APOE ϵ 4 carriers.	[33]

(continued)

Table 1
(Continued)

Study subjects (Sample size)	Study design	Biomarkers	Main outcome measured	Scientific Contribution	Reference
<i>New analytical techniques, animal model platforms, and software development</i>					
APPJ20/T64 mice and McGill-R-Thy1-APP rat	Animal model platform for AD	Brain imaging	Changes in PET imaging over time	Development of a platform for AD research using PET imaging and transgenic models	[25]
1,536 participants	Software development and validation	Computational cognitive battery	Cognitive decline	Development of a free platform for adults aged 40–90 to engage in cognitive training	[42]
273 samples	Software development and validation	Brain imaging	Voxel-wise changes brain imaging	A novel computational tool able to perform complex voxel-wise statistical in humans and animals	[43]
273 MCIs	Machine learning	[¹⁸ F]Florbetapir PET	Progression to dementia	The algorithm to predict incipient dementia with accuracy outperforming existing algorithms	[41]

Abbreviations: AD: Alzheimer's disease; APOE: apolipoprotein E; APP: amyloid precursor protein; bvFTD: behavioral version of fronto-temporal dementia; CN: cognitively normal; CSF: cerebro-spinal fluid; FDG: fluroro-deoxy-glucose; MAO-B: monoamine oxidase type B; MCI: mild cognitive impairment; MRI: magnetic resonance imaging; PET: positron emission tomography; PSP: progressive supra-nuclear palsy.

New analytical techniques and software development

The accuracy and optimization of neuroimaging methodological techniques is a special interest of our Center. Various different methods of analysis using neuroimaging modalities such as PET, MRI, and fMRI have been explored. For example, we have compared the accuracy of two widely used automated protocols (FreeSurfer and FSL) for MRI brain segmentation against the gold standard manual segmentation [40]. Using single A β PET information, we develop a novel analytical algorithm based on machine learning that outperformed all the existing algorithms using multiple biomarkers [41].

Website and software development in our Center has a significant impact. The Prevention Of Neurodegenerative Disease in Everyone at Risk (P.O.N.D.E.R) program was conceptualized to offer a free online platform for adults to participate in cognitive training and to be a large-scale tool to identify persons showing early signs of cognitive decline. 1,536 individuals have already signed up on the program's website (<http://ponder.mcgill.ca>) and underwent a standardized computerized battery assessing memory, executive function, attention, constructive abilities orientation, problem solving, language, and perception [42]. Additionally, in the neuroimaging field, our associates have developed

a singular computational framework that allows us to perform complex voxel-wise statistical operations with multiple scalar variables and image modalities at every brain voxel in humans and animal models [43].

Ethical issues in biomarker research

The ethical aspects associated with AD diagnosis and treatments have been a constant topic of interest in our center since its inception. More specifically, our research team have addressed ethical issues associated with the use of biomarkers in asymptomatic persons, very early disease diagnosis, and possibility of access to new treatments [44, 45]. Additionally, participation in the Ethical, Legal and Social Aspects (ELSI) committee of the Canadian Consortium of Neurodegeneration in Aging (CCNA) is a core part of our activities. This has facilitated the establishment of a trans-national scientific and ethics review for dementia research [46].

Education and knowledge transfer

One of the main aspects of our educational activities is the formation of the new generation of health professionals and researchers in AD. Every year, undergraduate, master, and doctoral students begin working on our project under the supervision of our members. In addition, our center receives a high flow

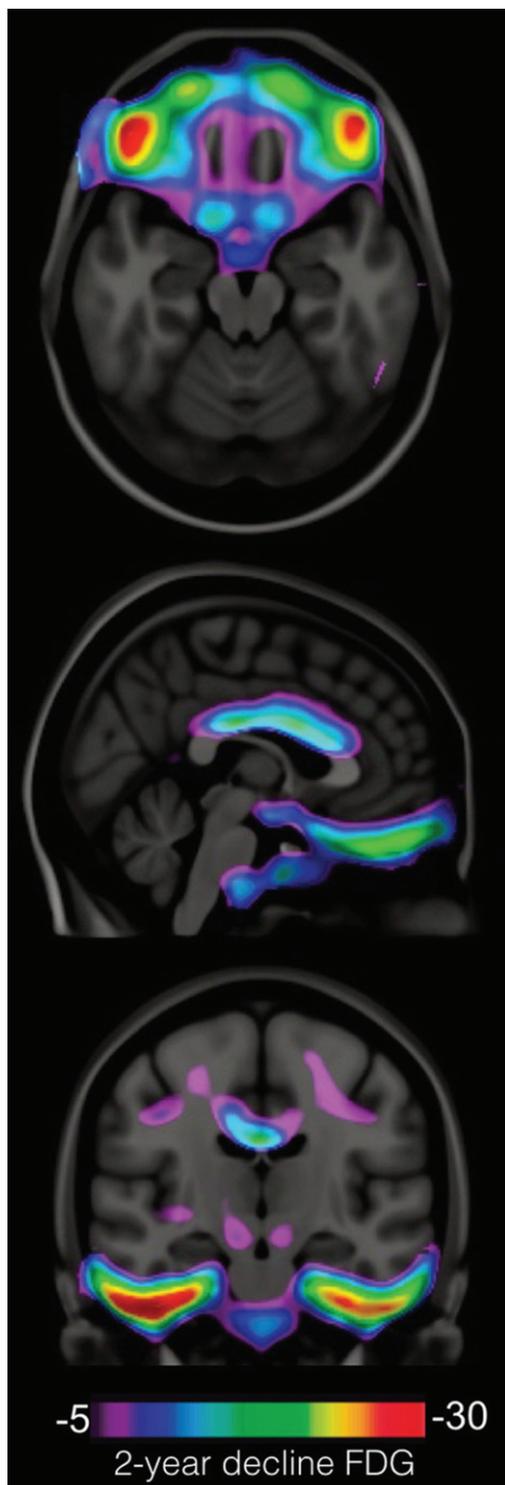


Fig. 1. Brain regions vulnerable to the synergy between $A\beta$ and tau in cognitively normal persons. The parametric map, overlaid in a structural MRI, revealed regions where 2-year $[^{18}F]FDG$ metabolic decline was associated with the synergistic effect between $A\beta$ and tau in cognitively normal elderly individuals.

of international students and visiting scholars who come as a complementary part of their studies to learn and share knowledge with our students and members. Seminars and lectures targeting AD relatives and the general public are also part of our work.

NEW DIRECTIONS

Drug discovery

The most recent review of the AD drug development pipeline demonstrated insufficient drug discovery activity to supply new agents for testing in RCTs [47], a concern previously noticed and blamed on the nosology and complexity of the biological mechanisms of AD (particularly in late onset with multiple co-morbidities), the low success of drugs for this condition, slow recruitment, and low retention for large scale RCTs in older persons [48]. Promising strategies to overcome these difficulties include sharing placebo groups, as currently done in the DIAN-TU RCTs, futility analysis, adaptive designs, patients, and volunteer registries. Another approach is to learn from the past RCTs about biological sub-groups of individuals responding to treatment. A good example is the ApoE4/4 carriers in the tramiprosate studies, which showed clinical stability over time compared to the overall group and the controls [49].

Biomarkers as a contribution to precision medicine in AD

Precision medicine is a concept which describes the biomarker guided identification of specific biological and molecular pathophysiologies in an individual with the aim of applying a personalized preventive or therapeutic approach which will more accurately target the particular biological dysfunction [50]. In a multifactorial disease such as AD, this investigation and therapeutic strategy is especially important as compared to the traditional “one pathophysiology fits all” approach. In this respect, the advancement of biomarkers research such as genetics, neuroimaging, and biological fluids, is expected to play an important role in decoding the specific pathophysiological alterations in each individual at risk for AD.

In line with precision medicine in AD where biomarker guided customized interventions may offer the best chance of therapeutic success, both

environmental and genetic factors have been included in recent clinical trials to enrich the study population with the highest risk of developing AD as soon as possible. For example, in the Alzheimer's Prevention Initiative (API) autosomal dominant AD trial, preclinical PSEN1 E280A mutation carriers have been recruited to study the efficacy and safety of crenezumab, while in the DIAN-TU trial, investigational drugs (gantenerumab and solanezumab) are being tested in individuals who either are known to carry a mutation, or are at risk due to a positive family history for a known AD-causing mutation in a parent or sibling, to evaluate these drugs impact on biomarker changes over time, and potentially demonstrating cognitive efficacy. In the API Generation study, CN healthy older adults who are at high-risk of developing AD based on their age (60–75 years) and genetic background (homozygous APOE4) are being recruited to study the cognitive efficacy of the active amyloid immunotherapy CAD106 or the beta secretase inhibitor 1 (BACE1) inhibitor CNP520 in preventing or delaying AD.

In these and future RCT targeting various pathophysiological factors at play in AD, biomarkers will play a major role in defining the populations to treat, and quantify the treatment response. With a bit of luck, we will be able to select the new drugs for the right patient at the right stage of disease, using individual biomarker profile.

Global perspective on AD prevention and treatment

From a global perspective, we need to learn from the success of therapies against cancer and infectious diseases, from a RCT design perspective [51] as well from a drug access perspective, when new therapies will have been demonstrated to be safe and effective [52]. Costs of earlier diagnosis are already being studied [53]. National dementia plans will have to adapt to new knowledge about early diagnosis and treatment as quickly as feasible once reliable scientific information has been disseminated.

CONCLUSIONS

Cautious optimism is appropriate for a near future (five years) time frame for a number of drugs acting on the different pathophysiological components of AD (amyloid deposition, tau hyperphosphorylation, neuroinflammation, vascular changes, to name the most important known so far). Since the relative

weight of these components will be different between individuals and will even change over time for each individual, a 'one drug fit for all' approach is no longer defensible. Precision medicine using biomarkers in the diagnosis and treatment of AD is the new strategy.

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