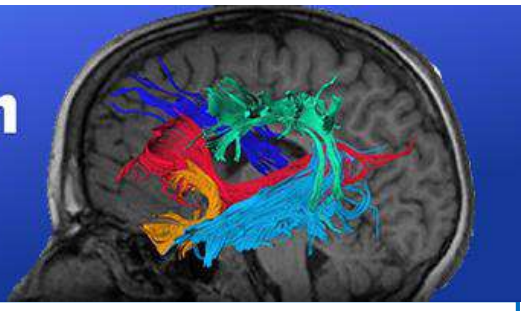
CCNA/CCNV Team 9 Bulletin

Biomarkers of Aging and Neurodegeneration

2020 Edition



Greetings from CCNA/CCNV Team 9

This newsletter is a periodic publication from Team 9 of the Canadian Consortium on Neurodegeneration in Aging (CCNA). It is produced and distributed by the Biomarkers Team leads, Roger A. Dixon (Alberta) and Pierre Bellec (Montréal). The major goal of this 2020 issue is to announce our exciting new partnership with Alberta Innovates and our new research goals for CCNA Phase II. We also offer brief updates on (1) Team 9 activities and emphases, (2) new members and collaborations, and (3) recent achievements of team members. Check page 2, as we seek input and offer opportunities for involvement in Team 9. We again thank Team 9 member Christian Beaulieu (Alberta) for the vivid diffusion MRI image displayed in the banner.

Roger A. Dixon and Pierre Bellec

Salutations de l'équipe CCNA/CCNV 9

Ce bulletin est une publication périodique issu de l'équipe 9 du Consortium canadien sur la neurodégénérescence associée au vieillissement (CCNV). Celui-ci est produit et distribué par les directeurs de l'équipe biomarqueurs, Roger A. Dixon (Alberta) et Pierre Bellec (Montréal). Le but principal de l'édition 2020 est d'annoncer notre nouveau partenariat avec Alberta Innovates et nos nouveaux objectifs de recherche pour la deuxième phase du CCNV. Nous offrons également de brèves mises à jour sur les sujets suivants: l'état des activités de l'équipe 9, la venue de nouveaux collègues au sein de l'équipe, nos collaborations ainsi que les réalisations récentes des membres de l'équipe. Veuillez consulter la page 2 car nous recherchons vos commentaires et offrons des opportunités de participer activement avec l'équipe 9. Nous remercions encore une fois Christian Beaulieu (Alberta), membre de l'équipe 9, pour nous avoir fourni l'image de l'IRM de diffusion affichée dans la bannière.

CIHR IRSC
Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

ALBERTA INNOVATES

CCNA CCNV
Canadian Consortium on Neurodegeneration in Aging / Consortium canadien en neurodégénérescence associée au vieillissement

Team 9 Members: Roger A. **Dixon** (Alberta), Pierre **Bellec** (Montréal), Aman **Badhwar** (Montréal), Robert **Bartha** (Western), Christian **Beaulieu** (Alberta), Sandra **Black** (Sunnybrook), Richard **Camicioli** (Alberta), Mallar **Chakravarty** (McGill), Ting-Huei **Chen** (Laval), Howard **Chertkow** (McGill), D. Louis **Collins** (McGill), Mari **DeMarco** (UBC), Simon **Duchesne** (Laval), Alan **Evans** (McGill), Esther **Fujiwara** (Alberta), Scott **Hofer** (Victoria), Zahinoor **Ismail** (Calgary), Yasser **Iturria-Medina** (McGill), Liang **Li** (Alberta), Nikolai **Malykhin** (Alberta), Mario **Masellis** (Sunnybrook), Joanne A. **Matsubara** (UBC), G. Peggy **McFall** (Alberta), Douglas **Munoz** (Queen's), Sridar **Narayanan** (BIC, McGill), Jacqueline **Pettersen** (UNBC), Marc J. **Poulin** (Calgary), Hyman **Schipper** (McGill), Eric **Smith** (Calgary), Peter **Stys** (Calgary), Sylvia **Villeneuve** (McGill), David **Westaway** (Alberta), David **Wishart** (Alberta).

CCNA Team 9: Transitioning from Phase I to Phase II

From its inception, the mission of the CCNA Biomarkers Team was to conduct multi-disciplinary research on aging and neurodegenerative disease that would accommodate a broad spectrum of biomarker domains and approaches. The team membership represents four major clusters of biomarker work: neuroimaging, neurobiological, neurocognitive, and neuro-quantitative. Unlike some CCNA teams, we do not have a single theme or specific goal (such as an RCT or principal clinical cohort). Our diverse membership employs approaches such as preclinical, experimental (hypothesis-guided), and large-scale (data-driven, including untargeted omics and machine learning technologies). However, a key Phase I goal was to advance the latter approach, as data-driven modelling of multi-modal biomarker data sets (ADNI, CCNA) is a strength of a large subset of Team 9 members. Phase II begins with the publication of a major Team 9 integrative review (connectomics, genomics, metabolomics) toward developing a machine-learning-based roadmap to biomarker detection and subtype discrimination.

Badhwar, A., McFall, G.P., Sapkota, S., Black, S., Chertkow, H., Duchesne, S., Masellis, M., Li, L., Dixon, R.A., & Bellec, P. (2020). A multiomics approach to heterogeneity in Alzheimer's disease: Focused review and roadmap. Brain. doi:10.1093/brain/awz384

Alberta Innovates: New Partner and New Opportunities for Biomarker Innovation

Team 9 is now funded by a unique partnership amongst Alberta Innovates, CIHR and CCNA, with fiduciary responsibilities shared by Baycrest Hospital (Toronto) and University of Alberta. The purpose of a generous investment by Alberta Innovates is to promote innovations in biomarker and subtype discovery, validation and translation through the application of Artificial Intelligence approaches, Machine Learning technologies, Neuroinformatics modeling, and Omics-based platforms in the field of aging and neurodegeneration. Team 9 will engage in capacity building within the province of Alberta as well as node development in Quebec (Pierre Bellec and others) and enhanced network engagement with Team 9 researchers in other provinces. We are very interested in identifying Team 9 members and trainees who would like to learn more about or participate in the exciting new initiatives. Please contact Roger Dixon (rdixon@ualberta.ca) for more information.

Sex and Gender Research in Team 9

CCNA, along with many funding organizations (CIHR, NIH), recognizes the importance of incorporating sex and gender in health and medical research. In CCNA the cross-cutting program on Women, Gender, Sex, and Dementia (WGSD) encourages researchers in neurodegeneration and dementia to apply these considerations. **Drs. Jacqueline A. Pettersen (UNBC/UBC) and G. Peggy McFall (Alberta), Team 9 WGSD liaisons, contributed the following article.**

The CCNA and Team 9 are committed to promoting research that includes analyses of sex and gender. Why are such analyses important? There are several important reasons, including the following: (1) Explanatory power—such analyses can help explain sex and gender differences in the condition under study, as well as the response to interventions; (2) Risk of harm—when research fails to account for sex and gender, there is a risk of harm by assuming that the study results apply to everyone; (3) Missed opportunities—We may miss critical opportunities to discover differences in the relationship between exposures and outcomes for men and women, which can inform opportunities for intervention; (4) Gender equity—We need to be able to understand the gender-related social factors that create differences in health outcomes between men and women, boys and girls, and gender-diverse people in order to address the underlying causes of inequity. More information about the CCNA WSGD program, led by Dr. Gillian Einstein (Toronto), may be found here (Webpage: https://ccna-ccnv.ca/women-gender-sex-dementia-wgsd/). Please feel free to contact Drs. McFall and Pettersen for information about (1) CIHR Sex and Gender Training modules, (2) Sex and Gender related literature, including recent reviews, (3) Advice for incorporating sex and gender into your research designs and manuscripts, (4) CCNA funding opportunities for sex and gender research, and (5) A growing list of related Team 9 studies.

Feature: Dr. Jacqueline Pettersen

A relatively new member of Team 9, **Dr. Jacqueline Pettersen** is a Cognitive/Behavioural Neurologist and Associate Professor with the University of British Columbia Northern Medical Program. She is particularly interested in vitamin D and its role in cognition and dementia. Her research has linked insufficient levels of vitamin D to worse cognitive performance, and also suggests that the optimal level for cognition is higher than the sufficiency levels currently recommended for bone health. Her recently published randomized trial in healthy adults revealed that higher dose vitamin D (4000 IU/d) results in improved visual (nonverbal) memory performance. She aims to further elucidate the importance of vitamin D in the development and progression of cognitive decline and dementia by examining relationships between vitamin D levels (and related markers) with neuropsychological and neuroimaging measures across and within the COMPASS-ND cohorts, accounting for possible modifying factors such as sex and APOE status. The COMPASS-ND design, with the substantial projected participants across diverse clinical cohorts, will offer a rich opportunity to study these relationships.

Sample Publication: JA Pettersen (2017). Does high dose vitamin D supplementation enhance cognition? A randomized trial in healthy adults. Experimental Gerontology, 90, 90-97. doi: 10.1016/j.exger.2017.01.019

Feature: New Team 9 Member Dr. Ting-Huei Chen

Dr. Ting-Huei Chen *is an Associate Professor in the Department of Mathematics and Statistics at Laval University and a member at CERVO Brain Research Center. She received her Ph.D. from the Biostatistics Department at the University of North Carolina at Chapel Hill and spent one year as postdoctoral fellow at National Cancer Institute.*

Her research interest is to develop new statistical methodology for genomics/genetics analysis. One of her recent works aimed to use multiple endophenotypes to better model the heterogeneous phenotypes of Alzheimer's disease (AD) to improve statistical power to identify the disease associated genetic factors [1]. Another one is the development of new polygenic risk score modelling techniques for disease risk prediction [2]. Our team member Ms. Mélissa Rochette is working on the identification of shared genetic factors and their functionality among AD and type-2 diabetes using genetic and image datasets.

Recent papers: [1] Chen et al (2020+) in press for Biometrics; [2] Chen et al (2020+) accepted for Journal of the American Statistical Association.

Feature: New Team 9 Member Dr. Yasser Iturria-Medina

Dr. Yasser Iturria-Medina is *an Assistant Professor at the Montreal Neurological Institute. He leads the Neuroinformatics for Personalized Medicine lab (http://www.neuropm-lab.com/), mainly supported by HBHL-McGill, FRQS, Weston Brain Institute, and Private Donors.*

We develop novel mathematical and computational models to predict disease course and identify individualized treatment profiles in neurodegeneration. By integrating multi-modal brain imaging and cognitive/clinical data, these mechanistic models characterize the multifactorial interactions of brain alterations (e.g., how misfolded proteins cause neuronal functional dysregulation and brain atrophy), the intra-brain spreading of associated pathological effects through brain connections (e.g., misfolded proteins and functional hyperactivity propagation), and the effects of therapeutic interventions to target disease evolution. We have also developed minimally-invasive blood-based biomarkers for patient diagnosis. By analyzing thousands of gene transcripts, our novel machine learning approach can detect individual disease states, effectively predicting neuropathological and clinical deterioration, while providing a comprehensive description of genes and molecular functions driving the neurodegenerative progression.

Recent papers: Iturria-Medina et al., 2020. Brain, 143(2), 661–673; Iturria-Medina et al., 2018. Neuroimage, 179, 40-50; Iturria-Medina et al., 2017. Neuroimage, 152, 60–77; Iturria-Medina et al., 2016. Nature Communications, 7, # 11934.

News: Team 9 Workshops

CCNA Neuroimaging Workshop (March 2019): This workshop co-organized by CCNA Trainee Society (Dr. AmanPreet Badhwar) and Team 9 (Dr. Pierre Bellec) was held at the Centre de recherche de l'Institut universitaire de gériatrie de Montréal. The goal was to bring together CCNA trainees and researchers to review and evaluate Team 9 imaging-related achievements in CCNA Phase I, and to propose goals and plans for Phase II. The workshop was structured as a half-day of formal presentations followed by a half-day of impromptu unconference sessions. Topics included (1) neuroimaging derivatives (from structural, functional and diffusion MRI data) to be released for the CCNA community, (2) possibilities for additional imaging modalities and quantitative modeling, and (3) multi-omics approaches that incorporate non-imaging biomarker modalities. The workshop, attended by 60 participants from multiple institutions in Quebec, Ontario and Alberta, provided an excellent opportunity for exchanges of ideas and networking opportunities. This event was funded by CCNA Trainee Society and CCNA Team 9.

Biomarker and Risk Factor Research in Aging and Neurodegenerative Disease: New Approaches, Promising Opportunities and Emerging Challenges (October 2019): This workshop was co-organized by Team 9 and ELSI (the CCNA Cross-cutting Program on Ethical, Legal and Social Implications) and presented twice at the CCNA Science Day in Quebec City. Four presenters included the co-organizers (Drs. Roger A. Dixon and Julie M. Robillard (ELSI)) as well as two CCNA early career members (Drs. Aman Badhwar and G. Peggy McFall). The purpose was to discuss the challenges encountered by researchers and clinicians in interpreting and returning complex and probabilistic biomarker results to participants and their families. The four presentations focused on: (1) Characteristics of contemporary multi-modal biomarker risk research, including omics and machine learning approaches (RAD), (2) Multi-omics approaches to AD biomarkers (AB), (3) Trajectory and subtype analyses with machine learning (GPM), and (4) The considerations required for communicating complex biomarker results (JMR).

Future Workshops: Several potential workshop topics are being developed by Team 9. Naturally, the timing and format (virtual, in-person) will depend in part on prevailing public health concerns. One potential in-person workshop is tentatively scheduled for October 2021. Team 9, in partnership with Alberta Innovates, will host a workshop on machine learning applications in research on biomarkers of neurodegeneration. Details will follow.

Selected Recent Biomarker Papers (Team 9 Members Listed)

HM Schipper, H Chertkow (plus co-authors): 2019. Development and validation of a salivary tau biomarker in Alzheimer's disease. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 11*, 53-60. doi:10.1016/j.dadm.2018.03.003

M Masellis, SE Black (plus co-authors): 2019. *APOE* ε4, white matter hyperintensities, and cognition in Alzheimer and Lewy body dementia. *Neurology, 93*(19), e1807-e1819. doi:10.1212/WNL.0000000000008377

ML DeMarco (plus co-author): 2019. The diagnostic performance of neurofilament light chain in CSF and blood for Alzheimer's disease, frontotemporal dementia, and amyotrophic lateral sclerosis: A systematic review and meta-analysis. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 11*, 730-743. doi:10.1016/j.dadm.2019.08.009

JA Matsubara (plus co-authors): 2018. Drusen in the peripheral retina of the Alzheimer's eye. *Current Alzheimer Research, 15*(8), 743-750. doi:10.2174/1567205015666180123122637

S Villeneuve (plus co-authors): 2020. Association of vascular risk factors with β-amyloid peptide and tau burdens in cognitively unimpaired individuals and its interaction with vascular medication use. *JAMA Network Open, 3*(2), e1920780. doi:10.1001/jamanetworkopen.2019.20780

A Badwar, S Duchesne, P Bellec (plus co-authors): 2020. Multivariate consistency of resting-state fMRI connectivity maps acquired on a single individual over 2.5 years, 13 sites and 3 vendors. *NeuroImage, 205*, 116210. doi:10.1016/j.neuroimage.2019.116210

SE Black, EE Smith (plus co-authors): 2019. Vascular dysfunction: The disregarded partner of Alzheimer's disease. *Alzheimer's & Dementia, 15*(1), 158-167. doi:10.1016/j.jalz.2018.07.222

D Westaway (plus co-author): 2020. Diverse, evolving conformer populations drive distinct phenotypes in frontotemporal lobar degeneration caused by the same MAPT-P301L mutation. *Acta Neuropathologica, 139*, 1045–1070. doi: 10.1007/s00401-020-02148-4

Acknowledgment: Team 9 (Dixon and Bellec) acknowledges the support of the CCNA/CCNV through funding from CIHR in partnership with Alberta Innovates (Ministry of Economic Development, Trade, and Tourism, Government of Alberta). Pierre acknowledges the support from the Courtois Foundation. Roger acknowledges leveraging with the NIH-funded Victoria Longitudinal Study.