CCNA/CCNV Team 9 Bulletin

Biomarkers of Aging and Neurodegeneration

Edition: June 2021

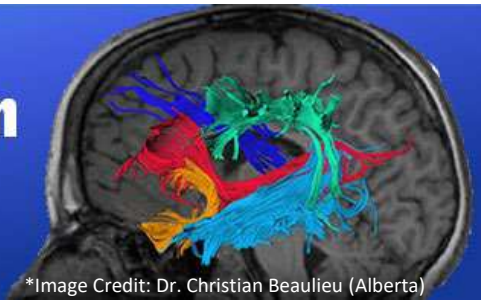


*Image Credit: Dr. Christian Beaulieu (Alberta)

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). In 2020 we announced a new Team 9 partnership with Alberta Innovates and CIHR in the context of CCNA. We are building a network within Team 9 for development and application of a variety of "neuroinformatics" approaches (omics, machine learning, big data, precision subtypes) in biomarker research. Notably, Team 9 continues to adhere to our four original goals: (1) Coordinate biomarker discovery and validation for multiple approaches, including both multi-site data-driven teams and individualized hypothesis-guided and mechanism-linked programs; (2) Contribute to core biomarker development in both neuroimaging and biofluid-based neurobiological modalities; (3) Initiate new synergistic and leveraging collaborations within and across CCNA teams, platforms and programs; and (4) Promote visibility, productivity, and functional participation in CCNA.

Roger A. Dixon and Pierre Bellec

Salutations de l'équipe CCNV/CCNA 9

Ce bulletin est une publication périodique issue 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 de biomarqueurs, Roger A. Dixon (Alberta) et Pierre Bellec (Montréal). Dans notre publication précédente, nous avons annoncé un nouveau partenariat avec Alberta Innovates et les IRSC dans le cadre du CCNV. Nous construisons un réseau au sein de l'équipe 9 pour le développement et l'application d'une variété de technologies neuro-informatiques (ex. omiques, l'apprentissage automatique, mégadonnées, sous-types de précision) pour la recherche de biomarqueurs. Notamment, l'équipe 9 continue d'adhérer à nos quatre objectifs initiaux : (1) Coordonner la découverte et la validation de biomarqueurs par l'entremise d'une variété d'approches avec des équipes multi-sites ayant comme objectif l'analyse axée sur les données ainsi que des programmes individualisés ayant comme fondation diverses hypothèses et mécanismes; (2) Contribuer au développement de biomarqueurs provenant de la neuroimagerie et des biofluides ; (3) Initier de nouvelles synergies et tirer parti de nos collaborations inter-équipes ainsi qu'à travers les diverses plateformes et programmes du CCNV ; et (4) Promouvoir la visibilité, la productivité, et la participation au sein du CCNV.

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

CCNA Canadian Consortium on Neurodegeneration in Aging

CCNV Consortium canadien en neurodégénérescence associée au vieillissement

ALBERTA INNOVATES

Team 9 Initiative: Developing a Network to Promote Neuroinformatics Applications to Biomarker Research in Aging and Neurodegenerative Disease

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. With a new partnership among CCNA, CIHR and Alberta Innovates, a key Phase II goal is to advance the application of Artificial Intelligence (including machine learning, data-driven approaches) for modeling multi-modal biomarker data sets in neurodegenerative diseases. We seek to access big (and small) data, explore and model data with machine learning technologies, and thereby (1) address heterogeneity in dementia and (2) move toward precision detection of subtypes and promotion of personalized interventions. CCNA members and trainees are invited to participate as we build a Team 9-based network for developing integrative approaches, scrutinizing novel platforms (e.g., omics), and generating new roadmaps to understanding and subtyping the spectra of aging and neurodegeneration.

New Research Progress: Team 9 Multi-Omics Biomarkers of Alzheimer's Disease Project

In CCNA Phase II, a major multi-site Team 9 project is underway. **Site 1 (Alberta)**: A team led by Roger Dixon and Liang Li is currently using new CIL-LC-MS technology to conduct both full metabolomics and lipidomics on two biofluid modalities across a spectrum of COMPASS-ND cohorts (cognitively normal, MCI, AD) in two phases (discovery, validation). **Site 2 (Montréal)**: A team led by Aman Badhwar will begin a proteomics analysis of plasma in the same AD spectrum cohorts. **Site 3 (Montréal, Laval)**: A team led by Pierre Bellec and Simon Duchesne will perform connectomics analyses, integrated with extant imaging markers, on the same cohorts. **First Outcome**: A novel made-in-CCNA multi-omics multi-modal biomarker profile of three cohorts will be produced and shared. **Second Outcome**: As described in the 2020 Team 9 "roadmap" article (BRAIN, PMID 31891371), we will integrate omics and machine learning to determine AD subtypes. **Next Steps**: We will conduct similar analyses on the (1) Mixed Etiology cohort (with collaborators H Chertkow, S Black, M Masellis, etc.) and (2) PD-LBD spectrum cohorts (with R Camicioli et al).

Trainee Transition: Congratulations to Dr. Shraddha Sapkota

Dr. Shraddha Sapkota is advancing to a new academic position with exceptional opportunities. A CCNA Team 9 trainee since her PhD program in neuroscience at the University of Alberta, Shraddha has been an Alzheimer Society of Canada/CCNA PDF at the Hurvitz Brain Sciences Research Program, Sunnybrook Research Institute, Toronto, where she was supervised by Team 9 members, Drs. Sandra Black and Mario Masellis. She will be an Assistant Professional Researcher in the Department of Neurology at the University of California, Davis. Her main affiliation will be with the Imaging of Dementia and Aging Laboratory (Director: Dr. Charles DeCarli). An example of recent work includes:

Sapkota, S., McFall, G.P., Masellis, M., Dixon, R.A., & Black, S. (2021). Differential cognitive decline in AD is predicted by changes in ventricular size but moderated by *APOE* and pulse pressure. [Data from the Sunnybrook Dementia Study; Manuscript to be submitted, Summer 2021]

Trainee Transition: Congratulations to Dr. AmanPreet Badhwar

Dr. AmanPreet Badhwar completed a post-doctoral fellowship in 2020 (supervisor: Dr. Bellec), with support from Alzheimer's Society and CIHR. She is now a Team 9 member and Assistant Professor with the Department of Pharmacology and Physiology at Université de Montréal, and a FRQS Chercheur Boursier Junior 1. Her Multiomics Investigation of Neurodegenerative Diseases (MIND) laboratory (https://badhwarmindlab.ca) integrates imaging and molecular 'omics' in the study of AD and other neurodegenerative diseases. Goals: (1) discovering new biomarkers and therapeutic targets, and (2) improving methods to speed the drug discovery process. Research example:

Badhwar, A., Haqqani, A.S. (2020). [Biomarker potential of brain-secreted extracellular vesicles in blood in Alzheimer's disease.] *Alzheimer's & Dementia (Amst).*, *12*(1), Article e12001. doi: 10.1002/dad2.12001

Feature: Lewy Bodies and Biomarkers: Collaborations by Teams 8 and 9

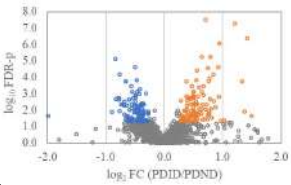
by Richard Camicioli (Alberta; Team 8 Lead; Team 9 Member); Krista Nelles (Alberta, Team 8 Coordinator)

Team 8 focuses on Parkinson's disease (PD) and Dementia with Lewy bodies (DLB), which represent a spectrum of aging disorders associated with cognitive and motor impairment. Notably, Lewy bodies are a co-pathology in Alzheimer's disease and contribute to about 50% of dementia cases. Teams 8 and 9 are natural collaborators in the context of CCNA, with its emphasis on the heterogeneity of neurodegeneration. The teams share interests in clinical, cognitive, motor, genetic, imaging and biofluid-based biomarkers, often in the context of omics and machine learning approaches. Although collaborations have leveraged data archives, including the CIHR-funded BioCog-PD study (RC PI), we are increasingly exploring the emerging Compass-ND data. We highlight three examples, each of which sets the stage for further CCNA work.

First, using BioCog-PD data, Team 8 collaborates with Alberta-based Team 9 members (Drs. Roger Dixon, Liang Li and Adrianna Buzatto) to establish the relevance of metabolomics (Han et al 2017) and lipidomics (Buzatto et al 2021) approaches for PD and DLB biomarker discovery, mechanistic pathway specification, and dementia prediction.

Second, the BioCog-PD cohort includes a spectrum similar to Compass-ND and hence offers an initial test cohort for specific and multi-modal biomarkers. The Montreal PD Risk of Dementia Scale (Team 8 member, Dr. Ron Postuma; Dawson et al 2018), has been validated by a Team 8 and 9 group (Linzy Bohn et al 2021). In addition, machine learning biomarker approaches are being applied to both BioCog-PD and Compass-ND PD and LBD data by the same group (Dr. G. Peggy McFall et al 2021).

Third, MRI neuroimaging markers in PD have been advanced. A shared postdoctoral fellow, Dr. Mahsa Dadar, working with Teams 8 and 9 (Dr. Simon Duschesne) examined the impact of white matter changes in DLB and their mechanisms using BioCog-PD and two open-source databases (PPMI and ADNI). Ongoing work is examining the neurodegenerative spectrum, clinical correlations, and developing novel templates and data analysis approaches in Compass-ND.



In summary, Team 8 and 9 collaborations highlight a key strength of CCNA – the facilitation of multidisciplinary research that is relevant to understanding these heterogeneous conditions and to people living with such dynamic and complex neurodegenerative disorders.

Bohn, L. et al. (2021). [The Montréal Parkinson Risk of Dementia Rating Scale, geriatric PD cohort.] (Submitted for Publication)

Buzatto, A.Z. et al. (2021). [Serum lipidomics detecting dementia in PD.] (Submitted for Publication)

Dadar, M. et al. (2021). [White matter hyperintensities, amyloid ß, PD.] *Parkinsonism Relat Disord*, *85*, 95–101. doi:10.1016/j.parkreldis.2021.02.031

Dawson, B.K. et al. (2018). [The Montréal Parkinson Risk of Dementia Scale.] *JAMA Neurol*, *75*(6), 704–710. doi:10.1001/jamaneurol.2018.0254

Han, W. et al. (2017). [Novel metabolic biomarkers for PD, metabolomics analysis.] *Mov Disord*, *32*(12), 1720–1728. doi:10.1002/mds.27173

McFall, G.P. et al. (May, 2021). [Machine learning, multi-modal predictors of dementia in PD.] Banff Virtual Dementia Conference, Alberta Canada.

Feature: Team 9 Member Dr. Maxime Descoteaux

Dr. Maxime Descoteaux has been Professor in Computer Science since 2009 at Sherbrooke University. He holds the Sherbrooke Institutional Research Chair in Neuroinformatics and is the founder and director of the Sherbrooke Connectivity Imaging Laboratory (SCIL) (http://scil.usherbrooke.ca/), where there are 15-20 graduate and medical students and postdocs. His background credentials include BSc and MSc degrees from McGill, a PhD in Computer Science from INRIA Sophia Antipolis – Mediterranée, and a postdoctoral position at NeuroSpin. His research focuses on brain connectivity, including state-of-the-art diffusion MRI acquisition, reconstruction, tractography, processing and visualization. Maxime publishes widely on these areas, with a current journal article count exceeding 125. One of his current projects is a collaboration with Team 9 members Drs. Christian Beaulieu (Alberta) and Simon Duchesne (Laval) on a CCNA diffusion MRI study. We welcome Maxime to CCNA Team 9, where he will play a major role in the development of the Team 9 Neuroinformatics Network.

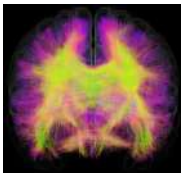


Image of Alzheimer's FDG-PET weighted structural connectome from: Roy, M. et al. (2021). [Ketogenic supplement improves white matter energy supply, processing speed in MCI.] *medRxiv*. doi:10.1101/2021.03.18.21253884

Theaud, G. et al. (2020). [TractoFlow: Robust, efficient, reproducible diffusion MRI pipeline leveraging Nextflow & Singularity.] *NeuroImage*, *218*, Article 116889. doi:10.1016/j.neuroimage.2020.116889

Descoteaux, M. et al. (2021). [How harmonized is a DTI harmonized protocol? Case study on SIMON pan-Canadian protocol.] (Manuscript in Preparation)

Report: Integrating Sex and Gender in Team 9 Research

CIHR, CCNA, and Team 9 are committed to promoting research that includes analyses of sex and gender. Dr. G. Peggy McFall (Alberta) and Dr. Jacqueline Pettersen (UNBC) are the Team 9 Champions for The Women, Sex, Gender & Dementia Program (WSGD; https://ccna-ccnv.ca/women-gender-sex-dementia-wgsd/), led by Dr. Gillian Einstein. We are available for questions about incorporating sex and gender into biomarker research and funding opportunities.

Watch for: WGSD sponsored conference on "*Why do more women than men get A*D?"

Suggested readings:

Nielsen, M.W. et al. (2021). Gender-related variables for health research. *Biology of Sex Differences, 12*, Article 23. https://doi.org/10.1186/s13293-021-00366-3; **Anstey, K.J. et al. (2021).** Sex differences in AD risk factors and memory decline, from ages 20 to 76. *Scientific Reports*, *11*, Article 7710. doi:10.1038/s41598-021-86397-7

Report: Important Contribution from Simon Duchesne (Team 9; Neuroimaging Platform)

In a fundamental contribution that will be relevant to many CCNA (COMPASS-ND) researchers, Dr. Simon Duchesne and colleagues have produced an open MRI tool to assess morphometric deviation from normality in adult brains. The tool—known as NOMIS—was developed on the basis of almost 7000 cognitively healthy adult participants in ADNI and CIMA-Q. Importantly, for its application to CCNA research with multiple clinical cohorts, NOMIS can account for (and investigate) differences in head size, age and sex. See link for further information.

https://www.biorxiv.org/content/biorxiv/early/2021/01/25/2021.01.25.428063.full.pdf

Report: Selected Outputs from Team 9 Members

*For recent reports to funders and partners, we have collected publications and other outputs from Team 9 members and trainees, often in collaboration with other CCNA members. The following list is an incomplete sampling. It is focused on Team 9 contributors (**in bold**). Please feel free to send us your CCNA Team 9-related outputs! For the newsletter, we welcome all related outputs. We note, however, that in official CCNA reporting only those outputs that acknowledge CCNA can be included.*

Anstey, K.; Authors include: **Dixon, R.A**. (2020). Future directions for dementia and prevention research…. *Journal of Alzheimer's Disease*, *78*(1), 3–12. doi:10.3233/JAD-200674

Badhwar, A.; Authors include: **Beaulieu, C., Chakravarty, M., Collins, L., Duchesne, S., Smith, E., Dixon, R.A., Bellec, P.** (2020). Standardized imaging derivatives in the COMPASS-ND cohort…. https://ccna-biomarkers.readthedocs.io/en/latest/

Badhwar, A.; Authors include: **Duchesne, S., Bellec, P.** (2020). Multivariate consistency of resting-state fMRI connectivity…. *NeuroImage*, *205*, Article 116210. doi:10.1016/j.neuroimage.2019.116210

Badhwar, A. McFall, G.P., Sapkota, S., Black, S., Chertkow, H., Duchesne, S., Masellis, M., Li, L., Dixon, R.A., & Bellec, P. (2020). Multiomics approach to heterogeneity in AD. *Brain*, *143*(5), 1315–1331. doi:10.1093/brain/awz384

Dadar, M.; Authors include: **Camicioli, R., Duchesne, S., Collins, D.L.** (2020). …white matter hyperintensities, neurodegeneration, amyloid beta, and cognition. *Alz & Dem*, *12*(1), Article 12091. doi:10.1002/dad2.12091

Dadar, M.; Authors include: **Duchesne, S., Camicioli, R.** (2020). Cognitive and motor correlates of grey and white matter pathology in Parkinson's disease. *NeuroImage: Clinical*, *27*, Article 102353. doi:10.1016/j.nicl.2020.102353

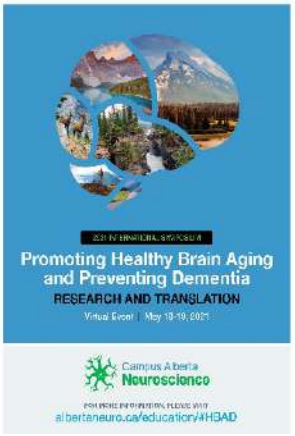
Drouin, S.M., McFall, G.P., & Dixon, R.A. (2020). In multiple facets of subjective memory decline, sex moderates memory predictions. *Alz & Dem: DADM*, *12*(1), Article 12089. doi:10.1002/dad2.12089

Montero-Odasso, M.; Authors include: **Ismail, Z., Camicioli, R.** (2020). Alzheimer disease, biomarkers, and clinical symptoms…. *JAMA Neurology*, *77*(3), 393–394. doi:10.1001/jamaneurol.2019.4959

Bohn, L.; Authors include: **McFall, G.P., Dixon, R.A.** (2021). Portals to frailty? Data-driven analyses detect early frailty profiles. *Alzheimer's Research and Therapy*, *13*, Article 1. doi:10.1186/s13195-020-00736-w

Matsubara, J.A. et al. (2021). Inhalable Thioflavin S for the detection of amyloid beta deposits in the retina. *Molecules*, *26*(4), Article 835. doi:10.3390/molecules26040835

KTE News: Team 9 Supports 2021 Banff (Virtual) Conference



Team 9 was active in the May 2021 version of the conference on **Promoting Healthy Brain Aging and Preventing Dementia: Research and Translation**, which was held virtually (instead of the traditional location in Banff, Alberta) this year. Highlights of the conference, once again sponsored by Campus Alberta Neuroscience, include the following:

- Four Alberta-based Team 9 members served in the Scientific Program Committee: Roger A. Dixon (Alberta), Marc Poulin (Calgary), Eric E. Smith (Calgary, Co-Lead Team 7), and David Westaway (Alberta), as well as Rob Sutherland (Lethbridge).
- Team 9 sponsored and RAD organized four talks for a session on: **Integrating Big Data, Neuroinformatics and Precision Health Approaches**:
  - David Wishart (Alberta, Team 9; ***Integrating Machine Learning, Omics Analyses, and Neurodegeneration***),
  - AmanPreet Badhwar (Montréal, Team 9; ***A Roadmap from Heterogeneity to Subtypes of ADRD***),
  - Yasser Iturria-Medina (McGill, Team 9; ***Multi-modal Biomarkers and Neuroinformatic Tools for Personalizing Treatments in Neurodegeneration***),
  - Michelle M. Mielke (Mayo Clinic; ***Combining Epidemiological and Precision Health Approaches to Understand Sex Differences in Alzheimer's Disease***).
- Other sessions included: **Applied Science and Intervention for Brain Health and Dementia** (organized by MP), **COVID-19 Effects on the Brain: Direct, Indirect and Persisting Consequences** (organized by EES), and **Challenges of Animal Models and Clarifying the Science Surrounding the Amyloid Hypothesis** (organized by DW).
- Keynote Speakers delivered two provocative talks:
  - Kaarin J. Anstey (UNSW, Australia: ***Will Promoting Brain Health Also Prevent Dementia?***)
  - Alison Goate (Icahn School of Medicine at Mount Sinai, New York: ***Human Genetics Implicates Microglial Function in Alzheimer's Disease Risk***).
- Other CCNA-related speakers included: Miia Kivipelto (Karolinska Institutet), Teresa Liu-Ambrose (UBC), Laura Middleton (Waterloo), and Dallas Seitz (Calgary).
- **Optimistic Note**: Campus Alberta Neuroscience is planning for the spring 2022 conference—live in Banff!

Team 9 Members: Roger A. **Dixon** (Alberta), Pierre **Bellec** (Montréal), AmanPreet **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), Maxime **Descoteaux** (Sherbrooke), 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), Josefina **Maranzano** (Québec à Trois-Rivières), Mario **Masellis** (Sunnybrook), Joanne A. **Matsubara** (UBC), G. Peggy **McFall** (Alberta), Douglas **Munoz** (Queen's), Sridar **Narayanan** (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).

Acknowledgment: **Team 9 (Dixon and Bellec) acknowledges the support of the CCNA/CCNV and partnership funding from Alberta Innovates (Ministry of Economic Development, Trade, and Tourism, Government of Alberta) and CIHR**. Pierre acknowledges support from the Courtois Foundation. Roger acknowledges leveraging with the NIH-funded Victoria Longitudinal Study and contributions from the SynAD Program (funded through a partnership with Alzheimer Society of Alberta and Northwest Territories and University Hospital Foundation). Thanks to Jill Friesen and Shannon Drouin for skilled technological assistance.