

Canadian Association of Gerontology 2019 Webinar Series

From animal models to older adult cohorts: clues to understand the processes of healthy aging

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No conflict of interest to declare



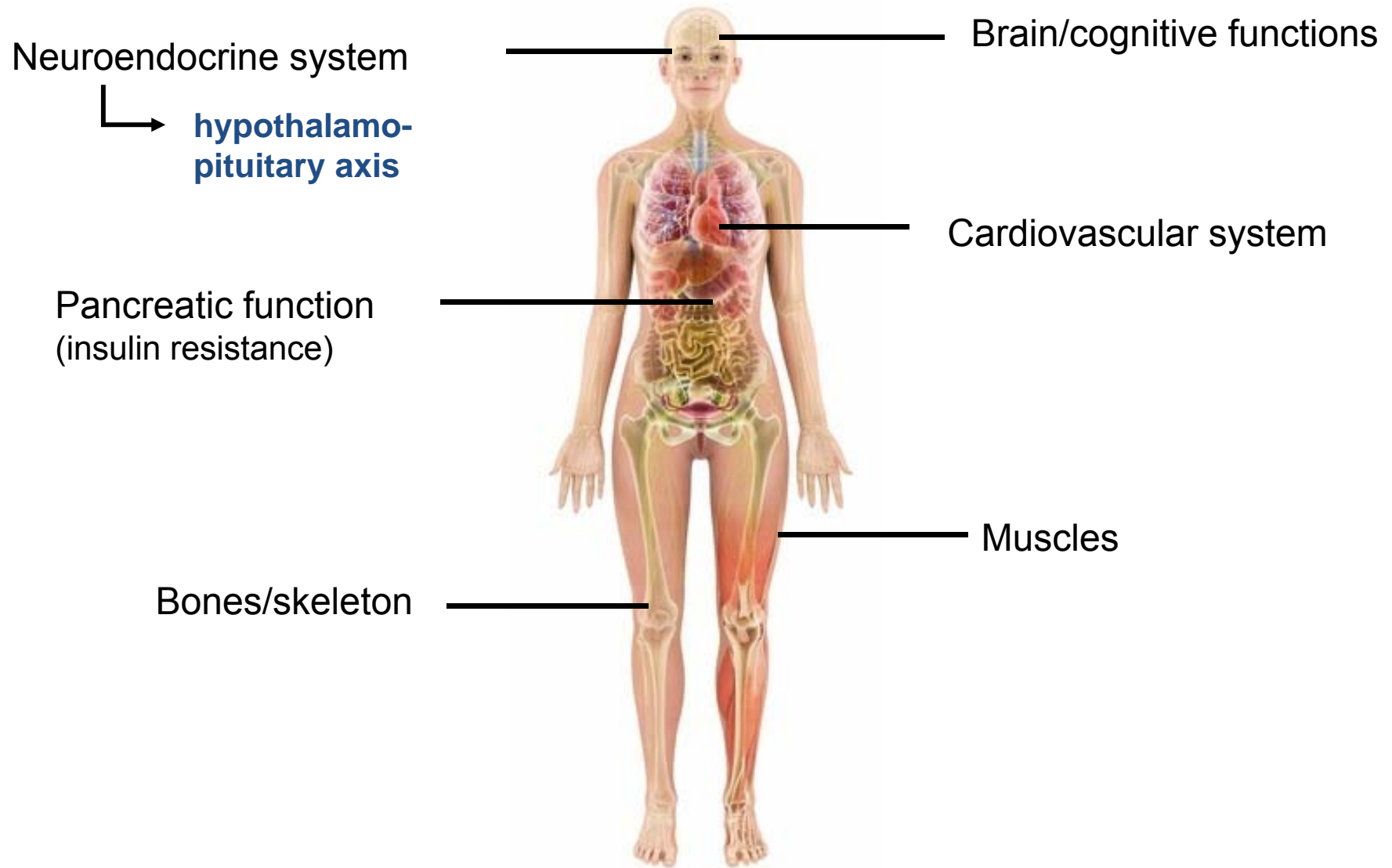
OUTLINE OF THE PRESENTATION



1. Introduction on aging
2. Results from preclinical modeling
3. Results from the older adult NuAge cohort

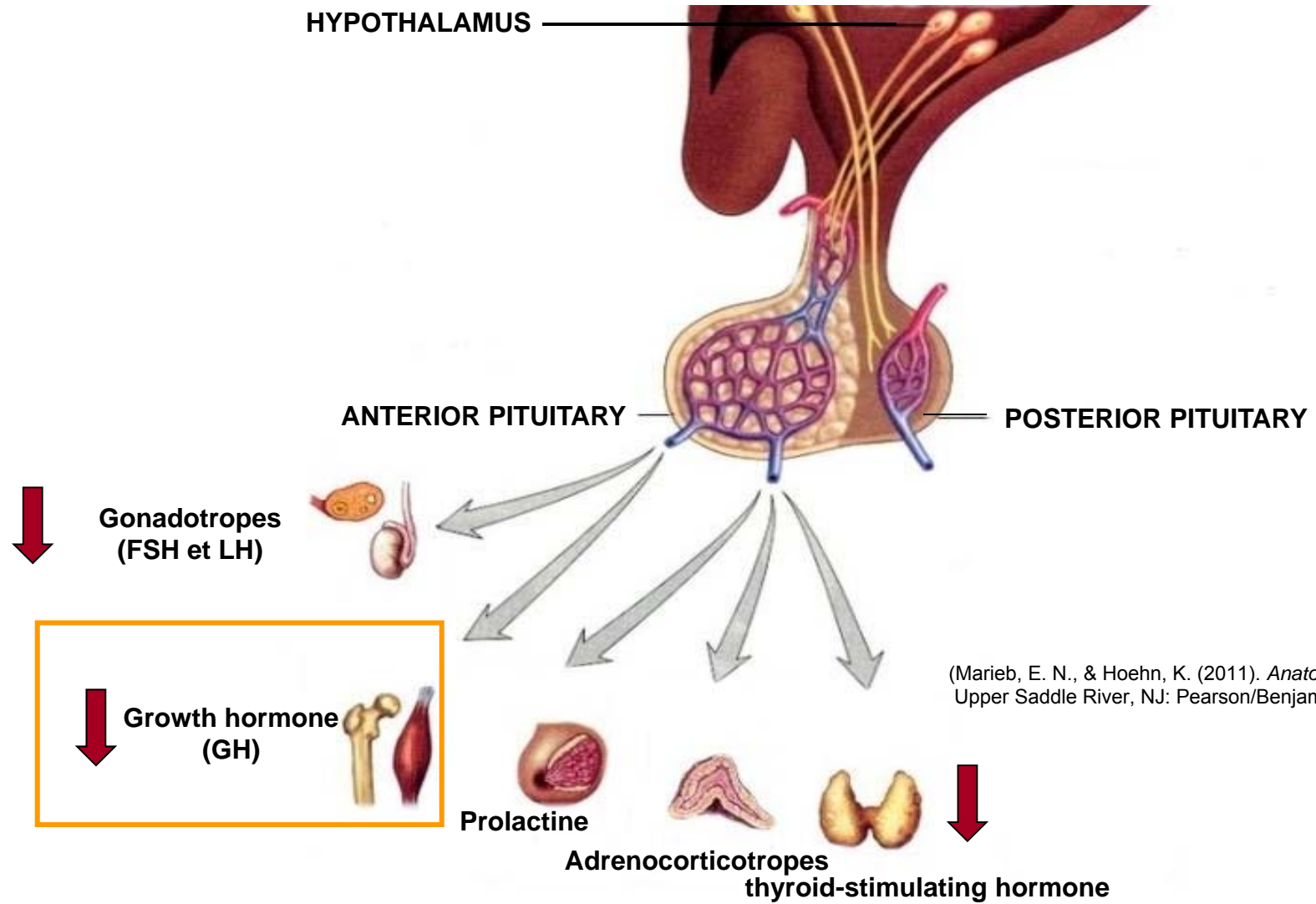


THE AGING PROCESS



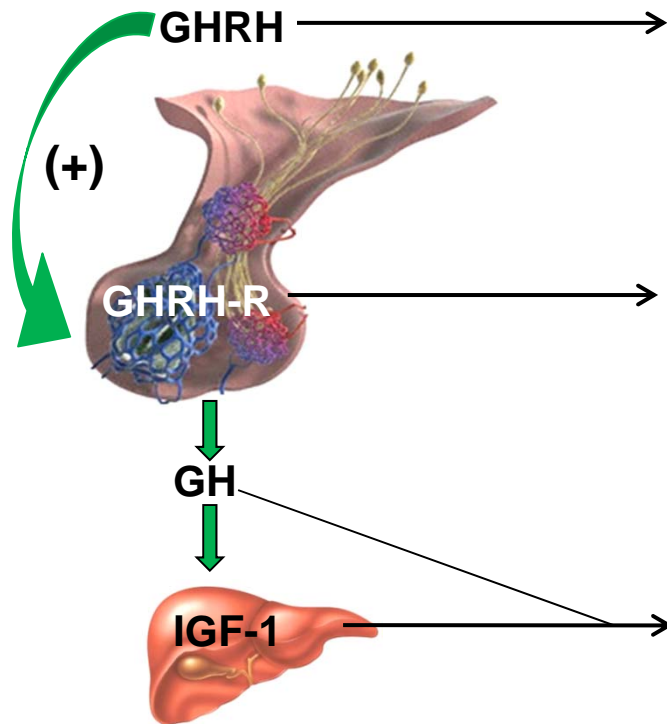


THE HYPOTHALAMO-PITUITARY AXIS





Dysfonction of the somatotroph axis leading to:



↓ GHRH mRNA levels (> 18 mois)

↓ Sensitivity of somatotropes to GHRH :

↓ Affinity and number of GHRH binding sites (8 mois)

↓ GHRH-R mRNA levels

↓ Circulating levels of GH and IGF-1 (12 mois)

Consequences...

↑ fat mass

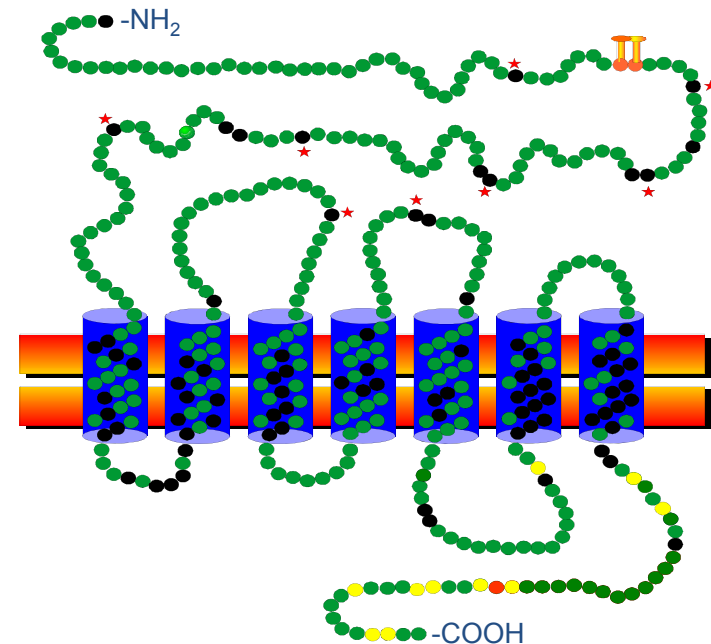
↓ muscle mass

Deterioration of several tissues and organs



THE GHRH RECEPTOR

- Cloning in 1992 (rat, mouse, human)
- 423-aa protein
- GPCR sub-family B-I
- N-terminus, extracellular loops and transmembrane domains required for GHRH binding
- C-terminus important for GHRH binding and GHRH-R activation
- Highest expression in the anterior pituitary



Adapted : Mayo et al. 1996, in Growth hormone secretagogues, Bercu BB and Walker RF Eds, Springer-Verlag, p.56.



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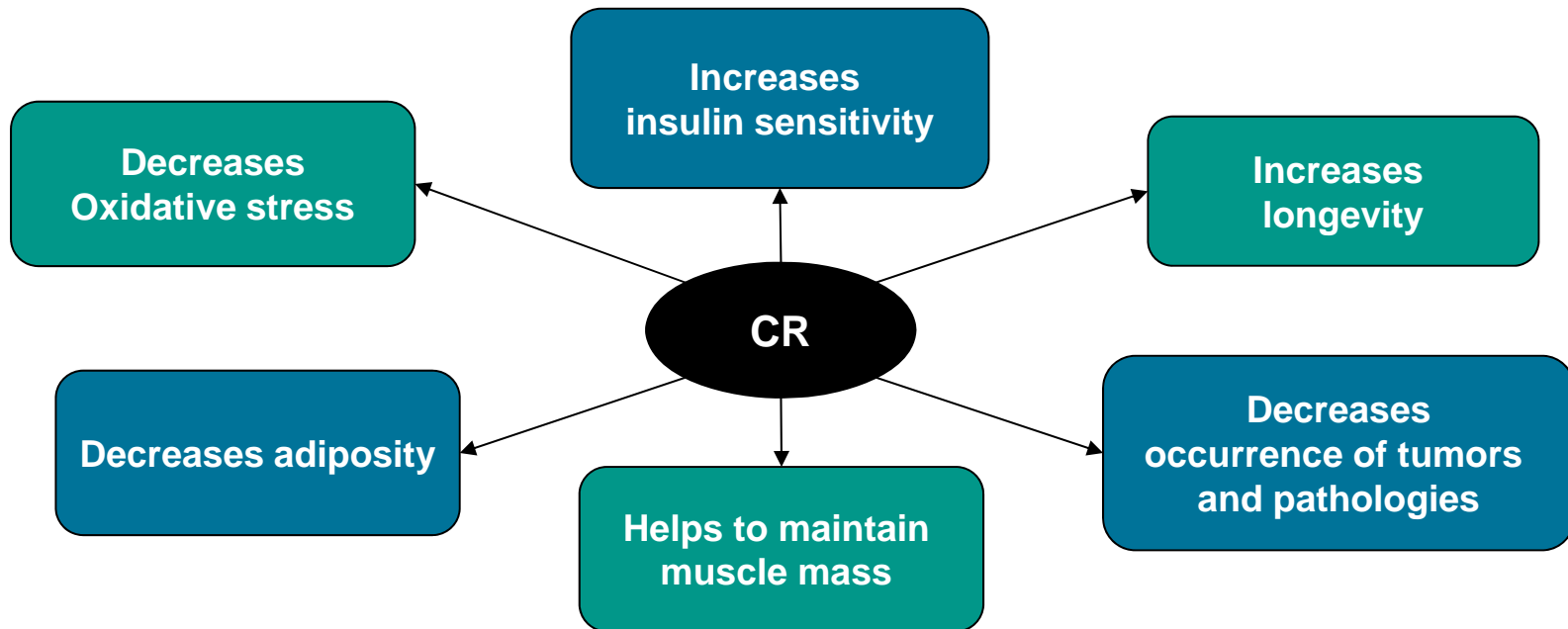
RESULTS FROM PRECLINICAL MODELS OF SUCCESSFUL AGING



LONG-TERM MODERATE CALORIE RESTRICTION

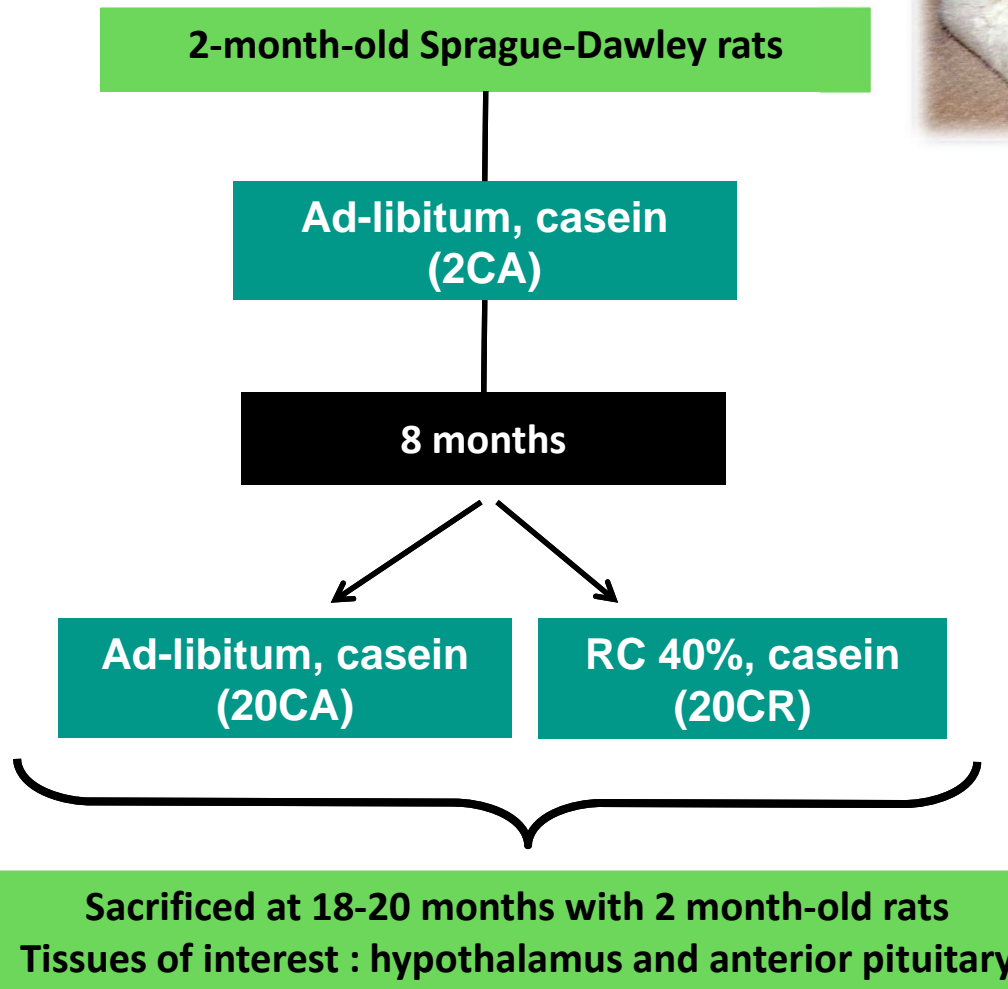
Long-term moderate calorie restriction is the most effective intervention to prevent or delaying age-related deterioration

Beneficial effects of CR in old rats





EXPERIMENTAL MODEL





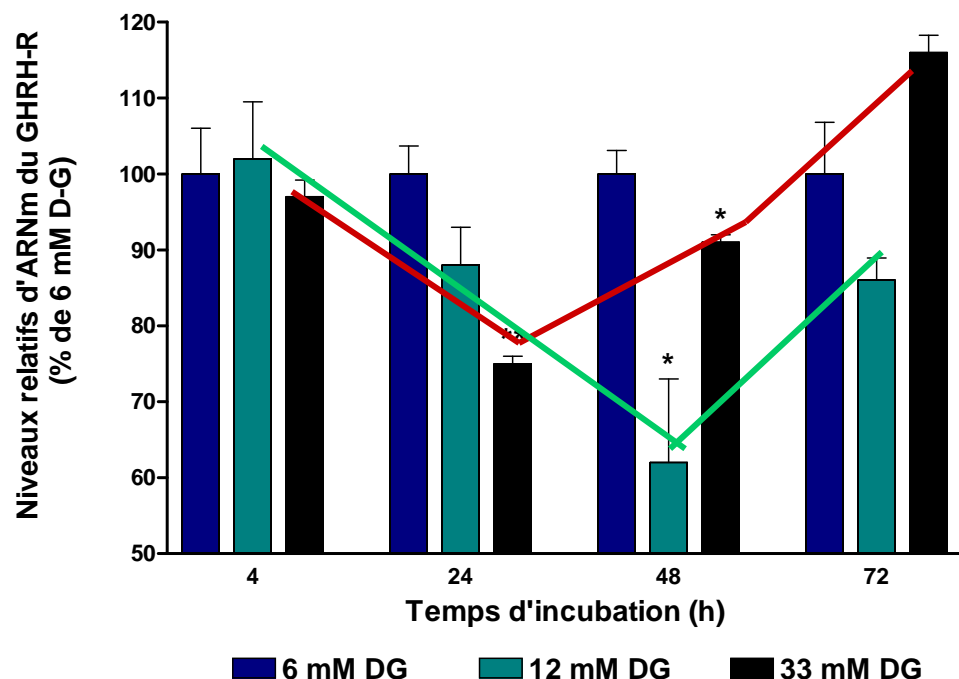
RESULTS

- LTMCR prevents the deleterious effects on GHRH-R associated with aging by increasing GHRH-R mRNA levels (2.5 kb)
- These transcriptional effects are accompanied by observed functional effects on GHRH binding parameters and maximal cAMP production stimulated by GHRH

It suggests:

With LTMCR: ↑ GHRH-R transcription translates to an ↑ of the number of functional GHRH-Rs, reflected in a maintenance of binding parameters and somatotropic sensitivity to GHRH

- Glucose and FFA are increased during aging and normalized by RCMLD
- They represent interesting candidates to study to better decipher the mechanisms of LTMCR



- GHRH-R mRNA levels are regulated according to duration and severity of glucotoxicity
- Alteration of the GHRH-R internalization process with 12 and 33 mM DG
- Decreased GHRH-stimulated cAMP production with 33 mM DG

Bédard et al, J.Am Physiol, 2008

Cellular glucotoxicity may be one of the mechanisms of GHRH-R dysfunction during aging

(Bédard et al, J Am Physiol, 2008)

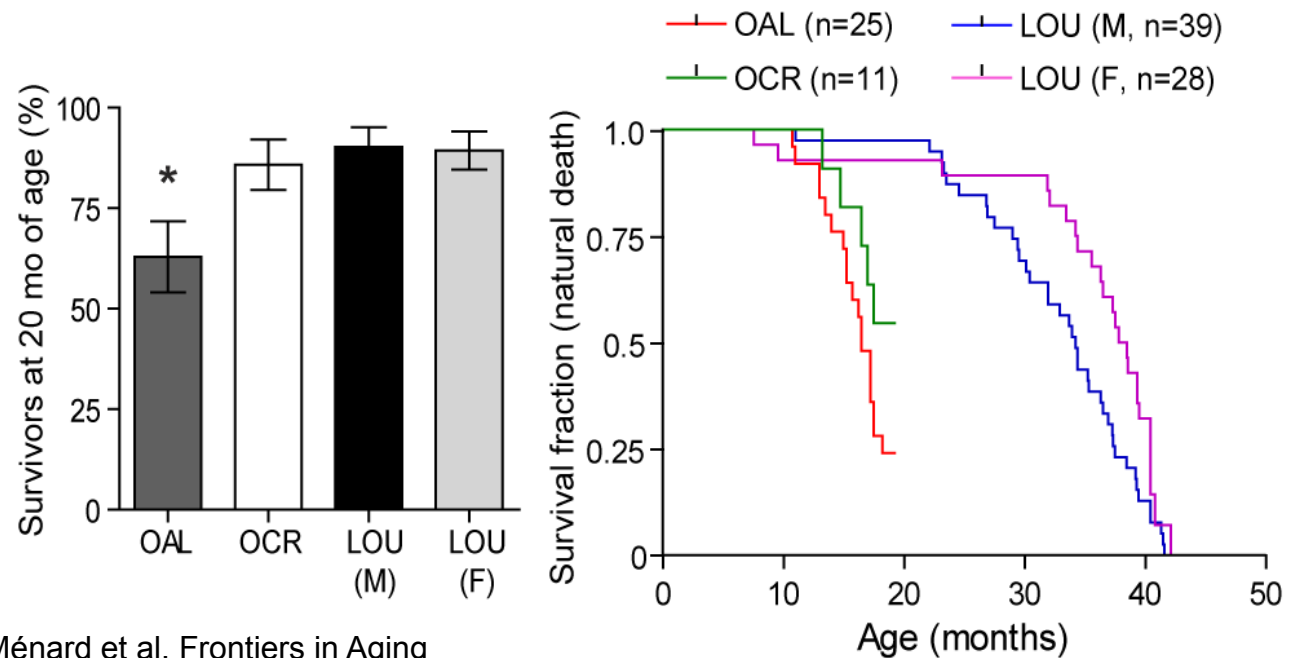


THE LOU RAT

The exceptional longevity in good health of the LOU rat:

- 90% of survivors at 20 months
- 50% of survivors at 29 months for males and at 33-34 months for female (*Alliot et al., 2002*)

LTMCR from 8 to 20
months increases
survival rate in SD rats



Ménard et al, Frontiers in Aging
Neurosciences, 2014



RESULTS



The aging LOU rat is characterized by:

- an increased longevity
- an absence of fat gain
- intact cognitive functions (reference and spatial memory)
- a low level of anxiety
- an intact brain plasticity comparable to that of young animals

- The LOU rat can therefore be considered as a model of successful aging
- Moderate long-term calorie restriction helps prevent some of the shortcomings associated with aging and obesity
- However, the performance and brain plasticity of the older LOU rat are superior, which raises the need to guide future research on understanding the underlying systemic and brain-specific mechanisms that ensure this successful aging

NUTRITION AS A DETERMINANT OF SUCCESSFUL AGING: THE QUEBEC LONGITUDINAL STUDY NUAGE

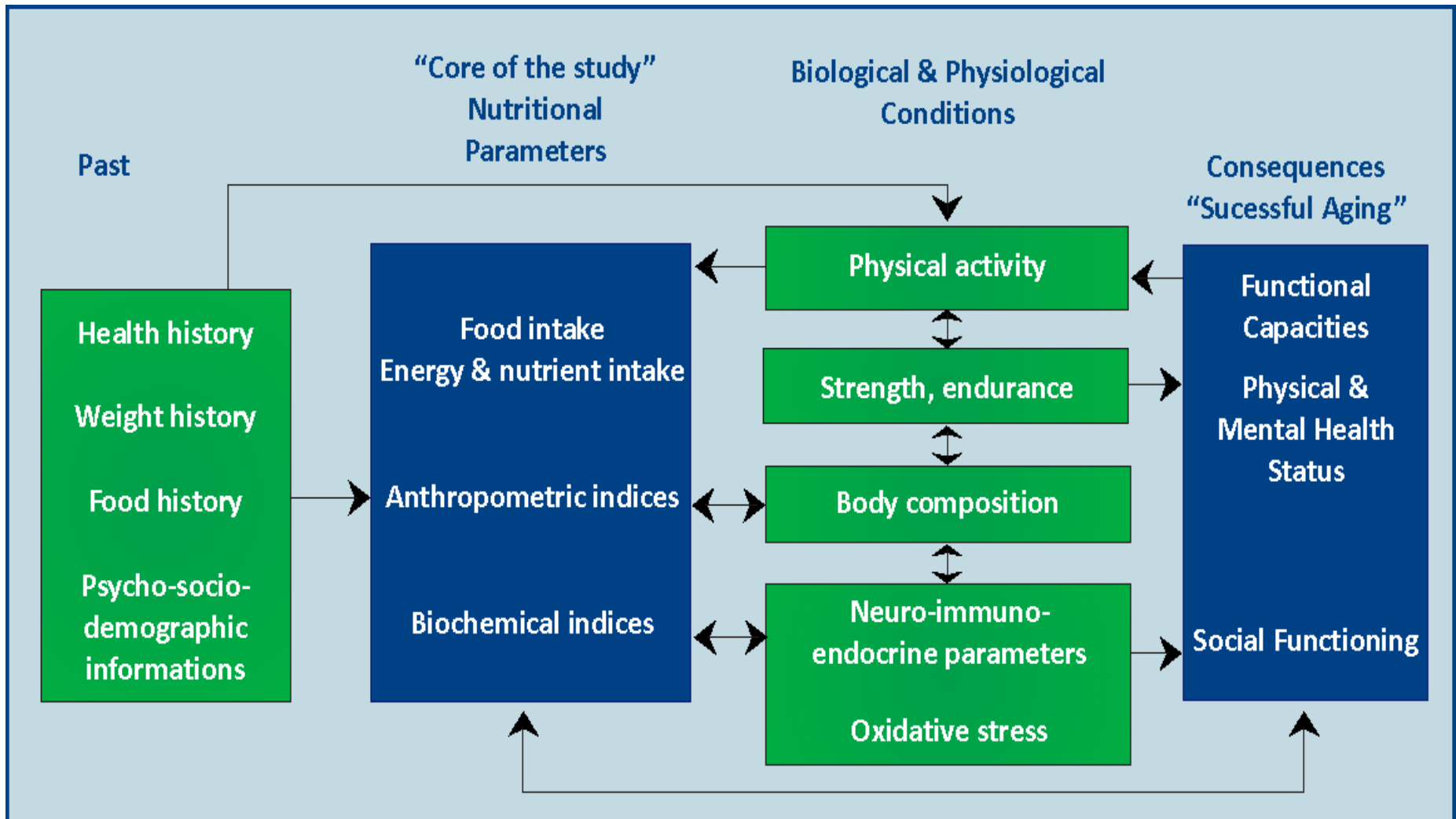
«An interdisciplinary and pluri-methodological
research program»

H Payette, P Gaudreau, K Gray-Donald, J A Morais, B Shatenstein
and Members of the thematic group on Nutrition,
Réseau Québécois de Recherche sur le vieillissement
University of Montreal, McGill University, Laval University
and University of Sherbrooke, Quebec, Canada





CONCEPTUAL FRAMEWORK





CHARACTERISTICS

- Pluridisciplinary and pluri-methodological approaches, including basic, clinical, epidemiologic and social research
- 1793 men and women, ~300/age group in 2003-2004, 68-72, 73-77, 78-82 years)
– large data bank and biobank (~ 500,000 samples of saliva, urine, serum/plasma, lymphocytes (DNA/RNA) processed to perform genomic, transcriptomic and proteomic analyses and to quantify several circulating biomarkers)
- Data on various facets of nutritional status (diet, food habits, appetite, anthropometry and body composition) and functional (muscle strength, physical activity, physical and functional capacities and performance), medical (physical, mental and cognitive health, medication) and social data (network, support, participation) collected by questionnaires and direct measurements
- **Several sub-studies conducted (e.g. NutCog, study of the impact of nutrition on cognitive functions)**
- **10-12-year telephone interview follow-up in 2014-2016**

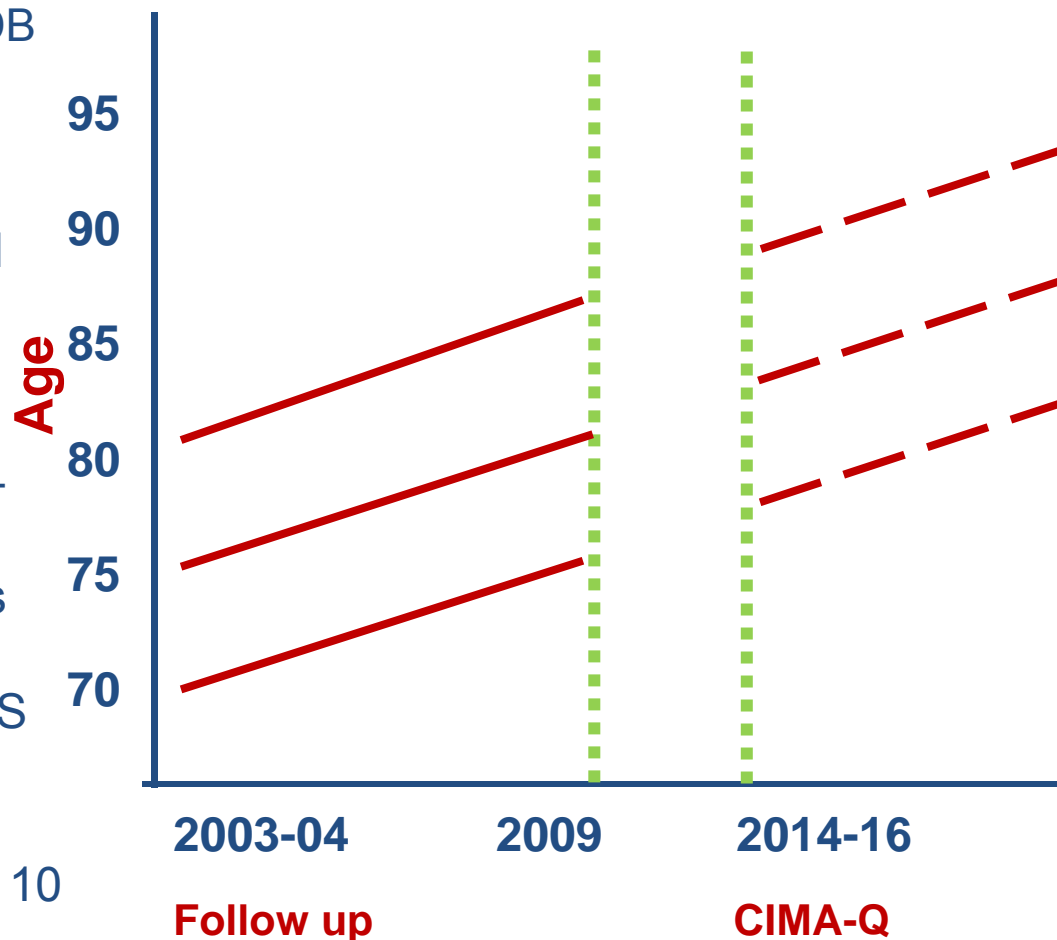


CHARACTERISTICS AND FOLLOW-UP

Random sample, stratified by age and sex, obtained from the Quebec Universal Health Insurance Plan DB

Inclusion criteria

- Community-dwelling men and women
- Aged 68-82 years
- French or English speaking
- Willing to commit for a 5 year-period
- Free of disabilities in activities of daily living
- No cognitive impairment (3MS >79)
- Able to walk without help
- Able to walk 100 m and climb 10 stairs without rest
- Able to sign an informed consent

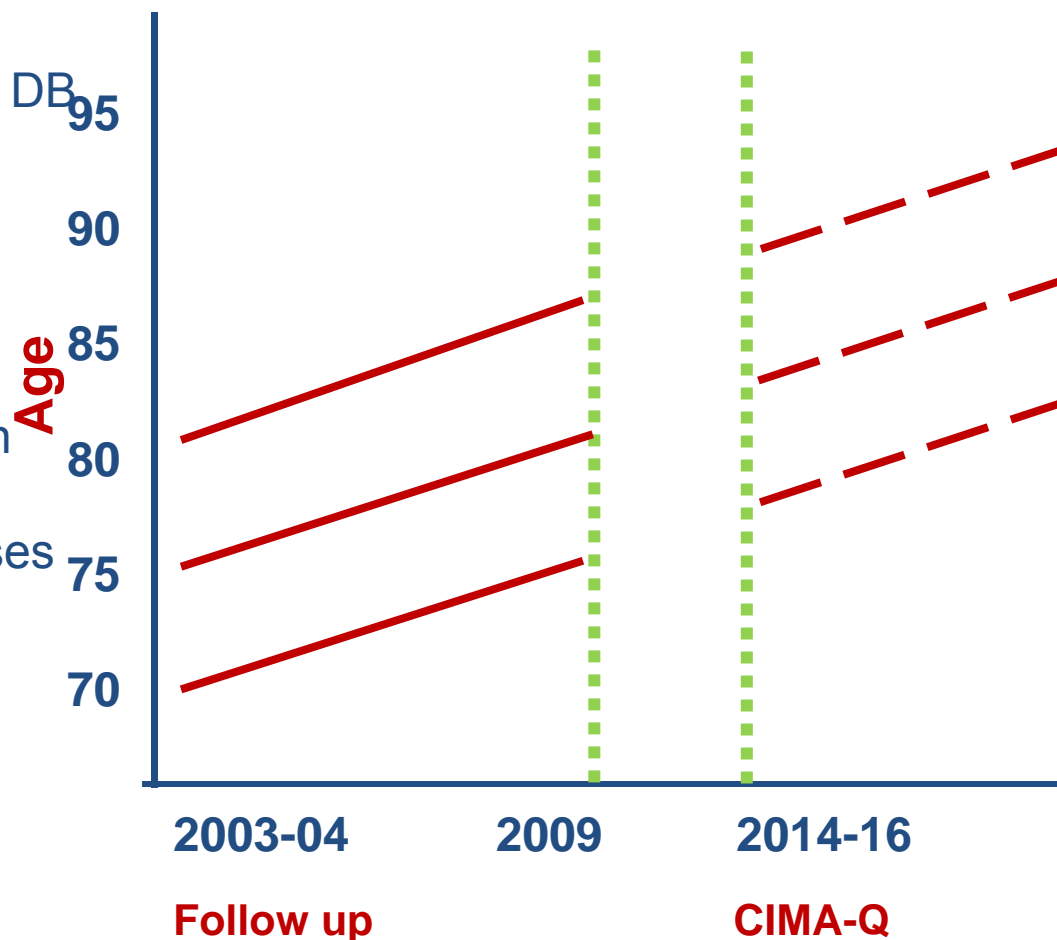




Random sample, stratified by age and sex obtained from the Quebec Universal Health Insurance Plan DB

Exclusion criteria

- Class II heart failure
- COPD requiring home oxygen therapy or oral steroids
- Inflammatory digestive diseases
- Cancer (radiation therapy, chemotherapy or surgery 5 previous years)





Computer-based data collection system > 1,000 variables/yr/participant

Nutritional: Diet, food habits and attitudes, sensory and physiological functions, anthropometry, body composition

Functional: Muscle strength, physical activity, performance, perceived capacities

Medical: Physical, mental and cognitive health

Social: Network, support, participation

Computerized-assisted system : biospecimen repository (>120,000 samples/yr)

Morning blood (50 ml) following an overnight fast (serum/plasma, peripheral lymphocytes for DNA/RNA)

Morning and evening saliva

Morning urine

Processed, aliquoted, bar-coded, kept frozen at -80°C



Cognition

1. T-MMSE: Telephone Mini-Mental State Examination (TMMSE®)
2. TICS: Telephone Interview for Cognitive Status™ (TICS™)

Other questionnaires

4. Elderly Nutrition Screening tool (ENS©) (malnutrition)
5. Perceived functional limitation (Nagi)
6. Autonomy in activities of daily living (ADL)



RESULT OVERVIEW

- 1793 participants at recruitment in 2003-2004
- **747 (41%)** were contacted in 2014-2016 (TICS, 2017)
- **585 (33%)** accepted to answer the various questionnaires (20-75 min): 257 men (44%), **328 women (56%)**
- **For the TICS, 373 (21%)**: 158 men (42%), **212 women (58%)**
- Age range on December 31st 2016 : **80-95 years (mean \pm SD = 86 \pm 4)**



RESULT OVERVIEW

Variable	niveaux	Tous n=585		Stratification par sexe			
		n	%	Hommes		Femmes	
		n	%	n	%	N	%
Sexe	M	257	43.9	-	-	-	-
	F	328	56.1	-	-	-	-
État civil à T4	Célibataire	37	6.8	8	21.6	29	78.4
	Veuf (ve)	132	24.4	18	13.6	114	86.4
	Marié(e)	338	62.4	197	58.3	141	41.7
	Séparé(e), Divorcé(e)	35	6.5	19	54.3	16	45.7



RESULT OVERVIEW

MÉTIER OU PROFESSION EXERCÉE LE PLUS LONGTEMPS N=585

	Tous		Hommes		Femmes	
	n	%	n	%	n	%
Tenir la maison	95	16.2	0	0.0	95	100
Travaux de la ferme	8	1.4	6	75.0	2	25.0
Professionnel	85	14.5	49	57.6	36	42.4
Administration, commerce	145	24.8	66	45.5	79	54.5
Technicien, auxiliaire	82	14.0	41	50.0	41	50.0
Ouvrier-manœuvre	86	14.7	56	65.1	30	34.9
Enseignement	56	9.6	24	42.9	32	57.1
Militaire	3	0.5	3	100	0	0
Autre	25	4.3	12	48.0	13	52.0
Total	585	100	257	43.9	328	56.1



RESULT OVERVIEW

➤ BW

- Men: 80-315 pounds, mean \pm SD = 170 \pm 28 pounds
- Women: 73-260 pounds, mean \pm SD = 140 \pm 27 pounds
- However, to the questions:
 - Did you loose weight over the last year: 57% of men and 43% of women said **YES**
 - Do you often have a good appetite: 46% of men and 54% of women said **YES**

➤ Elderly Nutrition Screening tool (ENS©) for malnutrition

- Score: 0 (best)- 8 (worse)
- Men: 0-7, mean \pm SD = 1.91 \pm 1.34
- Women: 0-8, mean \pm SD = 2.27 \pm 1.51



RESULT OVERVIEW

➤ **PERCEIVED FUNCTIONAL LIMITATION (Nagi)**

questionnaire; **example: are you able to raise your hands above the shoulders**)

- 1) Yes: with no difficulty or with a little difficulty or with some difficulties (scores 0-4)
- 2) Yes: with great difficulty or unable to do so or prohibited by the doctor (scores 5-6)
 - Men: 0-5, mean \pm SD = 0.35 ± 0.79
 - Women: 0-6, mean \pm SD = 0.56 ± 1.07

➤ **AUTONOMY IN ACTIVITIES OF DAILY LIVING (ADL** questionnaire)

- Score: 0 (worse)- 12 (best)
- Men: 7-12, mean \pm SD = 11.86 ± 0.62
- Women: 7-12, mean \pm SD = 11.78 ± 0.65



RESULT OVERVIEW

➤ TELEPHONE MINI-MENTAL STATE EXAMINATION (TMMSE)

- Score: 0 (worse) - 30 (best)
 - Men: 10-26, mean \pm SD = 21.94 \pm 2.87
 - Women: 9-26, mean \pm SD = 22.05 \pm 3.24
- Lower limit considered normal: 14.9-19.7 according to the education level

➤ TELEPHONE INTERVIEW FOR COGNITIVE STATUS (TICS)

- Score: 0 (worse) - 33 (best)
 - Men: 6-28, mean \pm SD = 16.08 \pm 4.76
 - Women: 4-33, mean \pm SD = 18.25 \pm 5.85
- **Poor scores for the TICS questionnaire. Long and difficult for NuAge participants** (Brandt J, Folstein MF: used for 60-98-year-old persons, Administration time, \leq 10 min).



COMING RESULTS

- To compare the T1-T4 trajectories (diet, exercise, social participation, chronic diseases, links between diabetic status and memory etc.) of these 585 participants with those of other NuAge participants that could not be recontacted
- To study the influence of gene polymorphisms as a **modulator** (Example: APOE 4/4 genotype)
 - The hypothesis being that lifestyle factors (mainly diet, exercise, social participation) influence positively and significantly healthy aging AND this relationship could be modulated by genotypic variations
- To define a metabolomics signature of metabolic syndrome in older adults (ongoing international study with researchers of the French MetaboHub)



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CONTRIBUTION TO GERONTOLOGY AWARD



On 20 October 2018, Dr. Pierrette Gaudreau was awarded the Contribution to Gerontology Award by the Canadian Association on Gerontology (CAG). The honorary plaque was presented by Professor Suzanne Dupuis-Blanchard (right), President of the CAG, at the 47th Annual Scientific and Educational Meeting. The CAG Awards were created to recognize individuals who contributed extensively in the field of gerontology. Pierrette Gaudreau earned this honor because of her outstanding contribution to the discipline of aging.