HABILITATION
À DIRIGER DES RECHERCHES

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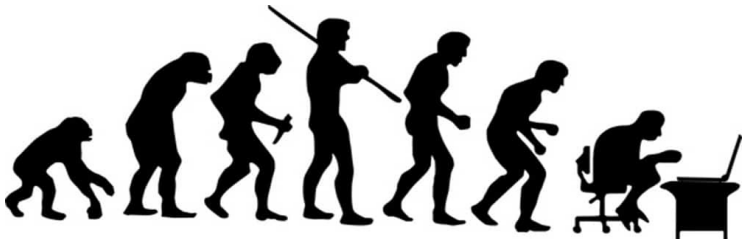
Ecologie de la santé :
La transition globale de l'activité physique



Le 14 Octobre 2019

Membres du Jury

Rapporteur Interne.....Fabrice FAVRET
Rapporteur Externe.....Yves BOIRIE
Rapporteur Externe.....Dylan THOMPSON
Examinateur.....Hélène BIHAN
Examinateur.....Emmanuelle CANET-SOULAS
Référent Scientifique.....Stéphane BLANC
Invité.....Daniel BESSESEN

Université de Strasbourg
Initiative d'excellence

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CURRICULUM VITAE

1. Professional trajectory

2018	Physiological Adaptations to Gravity & Health Team Leader, CNRS-IPHC UMR 7178
2017-22	Leader of the Joint International Laboratories (LIA) between the CNRS-IPHC UMR7178 & Univ. Colorado
2016	Permanent CNRS CR1 Researcher, CNRS-IPHC UMR7178, Strasbourg
	Affiliated Assistant Professor, Univ. Colorado and Colorado State University, USA
2015	Scientific Visitor, Baker IDI, Melbourne, Australia (3 months).
2014-16	Instructor, Univ. Colorado, USA
2014	Affiliated Researcher, Baker IDI Heart & Diabetes Institute, Melbourne, Australia
2013	Scientific Visitor, Baker IDI, Melbourne, Australia (9 months).
2009-13	Post-Doctoral Fellow, Univ. Colorado, USA
2008	PhD, Physiology & Organismal Biology, Univ. Strasbourg
2004	MSc, Ecophysiology & Energetics, Univ. Strasbourg

2. Awards & honors

2019	French Society for Nutrition (SFN) Award
2016	NORC Outstanding Fellow Award
	Clinical Research Award for Postdoc Research Day, Univ. Colorado
2015	NIH Best Program International Visiting Scientist Award, Univ. Colorado
2009	2008 Ph.D. Thesis Award, Univ. Strasbourg
2008	Sable Award for Young Researcher, RACMEM Congress
2006	CNES Young Researcher Award

3. Professional, consulting & community services

2021-	Organization Committee Member, Benjamin Franklin – Lafayette Seminar, Fréjus
2019-	Member of the Scientific Council for the IPHC-CNRS
2019-21	Expert for the European Space Agency (ESA) Topical Team "Space and Aging"
2019-24	Member of the Scientific Advisory Council of the French Space Agency (CNES)
2019-21	Member of the Steering Committee of the Doubly Labelled Water Core, Univ. of Colorado
2018	Chair, The Science of Sedentary Behavior and Health Meeting, Univ. Minneapolis
2017-19	Expert for the ESA Topical Team "Nutrition and Metabolism"
2017	Member of the Organization Committee Member, 3rd Congress of Animal Ecology (CEPA), Strasbourg
2012-16	Leader of the Anschutz Health & Wellness Center Post-Doc Association
2010-2012	Expert for the "Nutrition and Metabolism" Group for THESEUS : Towards Human Exploration of Space : a European Strategy Program (FP7).
2006	Member of the Organization Committee, 2nd European Congress on Ecology and Behavior (SERL), Strasbourg

4. Editorial activities

2019-	Review Editor, Frontiers in Nutrition: Nutrition & Metabolism
2019-21	Review Editor Fellow, Journal of Physiology (London)
2018-	Review Editor, Frontiers of Physiology: Environmental, Aviation & Space Physiology

5. Reviewing activities

For the last 3 years, I have reviewed 15-20 papers per year on average. Since 2009, I have frequently reviewed manuscript for the following journals:

Biochemical Journal
British Journal of Nutrition
Clinical Sciences

Diabetic Medicine
Diabetes
Diabetes Care
Endocrine Reviews
European Journal of Applied Physiology
Frontiers in Ecology and Evolution
Frontiers in Physiology
Frontiers in Public Health
International Journal of Environmental Research and Public Health
International Journal of Kinesiology
International Journal Obesity
Journal of Applied Physiology
Journal of Clinical Endocrinology & Metabolism
Journal of the International Society of Sports Nutrition
Journal of Nutrition
Medical Sport Science & Exercise
Metabolism
Microgravity – Science and Technology
Obesity
PloS One

2019	Review of research projects for the European Scientific Foundation (ESF)
2017-19	Review of the abstracts for The Obesity Society Annual Conference
2015	Review of research projects for the internal NIH/NIDDK grant system
	Review of research projects for Leakey Foundation
2011-18	Colorado Clinical & Translational Scientific Institute Review Panel Board

6. Invited talks at national and international conferences

2020	American College of Sport Medicine, San Francisco, CA, USA
	National Obesity Research Center, University of Birmingham, AL, USA
2019	Journées de Médecine Aéronautique et Spatiale, CNES, Toulouse, France
	Benjamin Franklin-Lafayette Seminar, Fréjus France
	The Obesity Society, Las Vegas, NV, USA
	Symposium "Exploring mechanisms linking Inactivity, Exercise and Cancer" University of Rennes, France
	Journées Francophones de Nutrition, Rennes, France
	Atelier Danone, Journées Francophones de Nutrition, Rennes, France
	Atelier Danone, Association Française de Pédiatrie Ambulatoire, Orléans, France
2018	International Human Space Flight Meeting, Toulouse, France
	Sedentary Behavior Council Workshop, ISPAH Conference, Cambridge, UK
2017	ILSI Focal Point in China, Chinese Center for Disease Control and Prevention, Beijing, China
	CNES Prospectives, CNES, Paris, France
	RACMEM, Fribourg, Switzerland
	Benjamin Franklin-Lafayette Seminar, Fréjus France
2016	Physiological Society Congress, Dublin, Ireland
	International Society for Gravitational Physiology, Toulouse, France.
	American College of Sport Medicine, Boston, MA, USA.
	CNES, Toulouse, France.
	Benjamin Franklin-Lafayette Seminars, Fréjus, France
2015	Dietary Mutations Workshop, CNRS, Paris
	French Space Agency, Toulouse, France
	American College of Sport Medicine, Indianapolis, IN, USA
2013	Denver Museum Nature & Science Conference
2012	3U Diabetes Conference: Current challenges in diabetes research, Dublin, Ireland.

7. National & International conferences

American College of Sport Medicine: 2011, 2017, 2019 (oral)
American Diabetes Association: 2015
American Physiology Society, the Integrative Biology of Exercise: 2012
American Society for Gravitational and Space Research: 2012
Biomedical research Conference: 2012
Canadian and European Space Agency Workshop: 2006 (oral)
Cell Symposium, Exercise Metabolism: 2019
Colorado School of Public Health: 2017 (oral)
COSPAR: 2018 (oral)
French Space Agency Young Researchers Conference: 2006
Human Space Flights Symposium: 2005
International Astronautical Congress: 2006 (oral)
International Journal of Behavioral Nutrition and Physical Activity Conference: 2019
International Society of Behavioral Nutrition and Physical Activity: 2019
International Society Gravitational Physiology: 2008 (oral), 2013 (oral), 2014 (oral), 2016 (oral)
International Society for the Measurement of Physical Behavior ICAMPAM: 2019 (oral)
JAXA CNES Workshop: 2017 (oral x 2)
POLAR: 2018 (oral)
RACMEM: 2008 (oral)
Société Française de Diabète: 2015 (oral), 2019 (oral)
The Endocrinology Society: 2012
The Obesity Society: 2010, 2013, 2019 (invited, oral, poster)
University of Colorado Postdoctoral Conference: 2015 (oral), 2016 (oral)

8. Jury/Committee/Teaching

2019	Jury member (examinateur), PhD Thesis Committee, Kevin Nay, Univ. Rennes
	Jury member (examinateur), PhD Thesis Committee, Blandine Charazin, Univ. Strasbourg, IPHC-CNRS
	Lecture (4h), Master Exercise Physiology, University of Clermont Ferrand, France
	PhD Thesis Committee, M Quque, 1st year, Univ. Strasbourg, IPHC-CNRS
	Lecture (2h), Master Human Bioenergetics, Colorado State University, USA
2018	Committee of pre-selection of external PhD applicants to Univ. Strasbourg Graduate School of Life Sciences
	Lecture (2h), Nutrition Seminars, Masters in Nutrition, Univ. Colorado
2017	Referee for Master's Theses in Animal Ecophysiology and Ethology, Univ. Strasbourg
	Jury member, Master 2 Animal Ecophysiology and Ethology, Univ. Strasbourg
2012	Jury member, Master in Global Health, Univ. Colorado
2009	Approval to apply to Assistant Prof. positions in French Universities in the research field of Physiology and Ecophysiology (Qualification)
2005-08	Master Lecture, Use of Stable Isotopes in Ecophysiology (4h/y), Univ. Strasbourg.
	Undergraduate Lecture, Doubly Labeled Water Method (2h/y), Univ. Strasbourg.
	Undergraduate Class, Physiology of Invertebrates (20h/y), Univ. Strasbourg.

9. Mentoring & co-mentoring experience

Post-doc fellows	C Laurens, CNES postdoctoral fellowship (2018-2020, co-mentor: S. Blanc)
	- *Travel Award from the French Society for Diabetes*
	E Cohen, CNRS Labex DRHIM postodoctoral fellowship (2019, co-mentor: S. Blanc)
PhD Students	Elisa LeRoux, CNRS Pre-doctoral scholarship (IPHC-CNRS, 2019-2022)
	P Bourdier, Univ. Strasbourg Graduate School of Life Sciences pre-doctoral scholarship (IPHC-CNRS, 2019-2022)
	N DeJong, NIH NIDDK R00 award (Colorado State University, 2016-present, co-mentor: M. Hickey)
	- *2016 Outstanding Platform Oral Presentation Award of the Colorado School of Public Health*

- *2018 Colorado National Obesity Research Center Outstanding Graduate Student Award*
- *Selected to attend graduate courses at the Pennington Biomedical research Center*
- *NIH Pre-doctoral TL1 Fellowship*

I Debache, ANR (Univ. Strasbourg, 2017-present, co-mentor: C. Sueur)
M Garnotel, CIFRE (Univ. Lyon, 2016-2019, co-mentors: C. Simon & S. Blanc)
A Damiot, CNES doctoral fellowship (Univ. Strasbourg, 2015-2018, co-mentors: C. Simon & S. Blanc)
F Rudwill, CNES doctoral fellowship (Univ. Strasbourg, 2009-2012, co-mentors: C. Simon & S. Blanc)

- *2014 ISGP meeting Young Researcher Award*

Master

L Schreck, CSU MS Exercise Physiology Program (2018-2019)

- *Travel Award from the ACSM, oral presentation*

H Hamidu (Regis Univ. MS Biomedical Sciences, 2017-2018)
A Lange (Regis Univ. MS Biomedical Sciences, 2016-2017)
T Glazer (Regis Univ. MS Biomedical Sciences, 2016-2017)
R Foright (Univ. Colorado MS Integrative Physiology, 2015)

Undergraduates

L Schreck (CSU, Human Bioenergetics, 2017-2018)
C Mendez (Denver Metro Univ., 2016-2017)
Andre Chavez (Brasilian Medical School Exchange Program, 2014)
K Monclova-Camacho (The Endocrine Society, 2012)

- *Award of the Best Student presentation at the Endocrine Society*

A Bent (IUT Biologie de Strasbourg, 2006)

10. Publications

- **Articles published in peer-reviewed journals**

*[S]Students or post-doctoral fellows, *1st co-authors, [#]last co-authors*

1. Halliday T, Rynders CA, Thomas EA, **Bergouignan A**, Pan Z, Kealey EA, Cornier LA, Bessesen DH. Appetite-related responses to overfeeding and longitudinal weight change in obesity prone and obesity resistance adults. Obesity, *in press*

2. Roth JD, Dobson FD, Criscuolo F, Uhlrich P, Zahariev A, **Bergouignan A**, Viblanc VA. Subtle short-term physiological costs of an experimental augmentation of fleas in wild Columbian ground squirrels. J Exp Biol. 2019 May 28. pii: jeb.203588. doi: 10.1242/jeb.203588. PMID: 31138632

3. Grace MS[S], Formosa MF, Bozaoglu K, **Bergouignan A**, Brozynska M, Carey AC, Bertuzzo Veiga C, Sethi P, Dillon F, Bertovic DA, Inouye M, Owen N, Dunstan DW, Kingwell BA. Acute effects of active breaks during prolonged sitting on subcutaneous adipose tissue gene expression: an ancillary analysis of a randomized controlled trial. Scientific Reports 2019 Mar 7;9(1):3847.

4. Laurens C[s], Simon C, Vernikos J, Gauquelin-Koch G, Blanc S, **Bergouignan A**. Revisiting the role of exercise countermeasure on the regulation of energy balance during space flight. Frontiers in Physiology: Exercise Physiology, 2019 Mar 29;10:321

5. Debache I[S], **Bergouignan A**, Sneekes EM, Chaix B, Sueur C. Associations of a sensor-derived physical behavior with metabolic health: a compositional analysis in the RECORD Multisensor Study. Int J Envir Res Pub Health, 2019 Mar 1;16(5). pii: E74

6. Ostendorf D, Caldwell AE, Creasy SA, Pan Z, Lyden K, **Bergouignan A**, MacLean PS, Wyatt HR Hill JO, Melanson EL, Catenacci VA. Physical Activity Energy Expenditure and Total Daily Energy Expenditure in Successful Weight Loss Maintainers. Obesity, Mar;27(3):496-504. ***Editorial pick-up***

7. DeJong N[S], Rynders CA, Goldstrohm DA, Pan Z, Lange AH[S], Mendez C[S], Melanson EL, Bessesen DH[#], **Bergouignan A[#]**. Effect of frequent interruptions of sedentary time on nutrient metabolism in sedentary overweight male and female adults. J Appl Physiol (1985). 2019 Apr 1;126(4):984-992.

8. Wilhelmi de Toledo F, Grundler F, **Bergouignan A**, Drinda S, Michalsen A. Safety, health improvement and well-being during a 4 to 21-day fasting period in an observational study including 1422 subjects. PLoS One. 2019 Jan 2;14(1):e0209353.

9. DeJong N[S], Debache I[S], Pan Z, Garnotel M, Lyden K, Sueur C, Simon C, Bessesen DH[#], **Bergouignan A[#]**. Breaking up Sedentary Time in Overweight/Obese Adults on Work Days and Non-Work Days: Results from a Randomized Feasibility Study. Int J Envir Res Pub Health, 2018 Nov 16;15(11).

10.Rynders CA, Pereira R, **Bergouignan A**, Kealey E, Bessesen DH. Associations among dietary fat oxidation responses to overfeeding and weight gain in obesity-prone and resistant adult. Obesity, 2018 Nov;26(11):1758-1766. ***Editorial pick-up***

11.Damiot A[S], Demangel R, Noone J, Chery I, Zahariev A, Normand S, Brioche T, Crampes F, de Glisezinski I, Lefai E, Bareille MP, Chopard A, Drai J, Collin-Chavagnac D, Heer M, Gauquelin-Koch G, Prost M, Simon P, Py G, Blanc S[#], Simon C[#], **Bergouignan A[#]**, O'Gorman D[#]. A nutrient cocktail prevents lipid metabolism alterations induced by 20 days of daily steps reduction and fructose overfeeding: Results from a randomized study. J Appl Physiol (1985). 2018 Oct 4.

12.Creasy SA, Rynders CA, **Bergouignan A,** Kealey EH, Bessesen DH. Free-living responses in energy balance to short-term overfeeding in adults differing in propensity for obesity. Obesity (Silver Spring). 2018 Apr;26(4):696-702. ***Editorial pick-up***

13.Foright RM[S], Presby DM, Sherk VD, Kahn D, Checkley LA, Giles ED, **Bergouignan A**, Higgins JA, Jackman MR, Hill JO, MacLean PS. Is regular exercise an effective strategy for weight loss maintenance? Physiol Behav. 2018 May 1;188:86-93.

14.Rudwill F[S]*, O'Gorman D*, Lefai E, Chery I, Zahariev A, Normand S, Pagano AF, Chopard A, Damiot A, Laurens C, Hodson L, Canet-Soulas E, Heer M, Frings Meuthen P, Buehlmeier J, Baecker N, Meiller L, Gauquelin-Koch G, Blanc S[#], Simon C[#], **Bergouignan A[#]**. Metabolic inflexibility is an early marker of bed-rest induced glucose intolerance even when fat mass is stable. J Clin Endocrinol Metab. 2018 Mar 12.

15.Rynders CA, Schmidt SL, **Bergouignan A**, Horton TJ, Bessesen DH. Effects of short-term sex steroid suppression on dietary fat storage patterns in healthy males. Physiol Reports, 2018 Jan;6(2).

16.Rynders CA, Blanc S, DeJong N[S], Bessesen DH, **Bergouignan A**. Sedentary behaviors as a key determinant of metabolic flexibility. J Physiol, 2018. ***Review on invitation***

17.Lefai E*, Blanc S*, Antoun E, Momken I, Chery I, Zahariev A, Gabert L, **Bergouignan A[#],** Simon C[#]. Exercise training improves fat metabolism independent of total energy expenditure in sedentary overweight men, but does not restore lean metabolic phenotype. Int J Obes (Lond). 2017 Jul 3.

18.Rynders CA, **Bergouignan A,** Kealey E, Bessesen DH. Ability to adjust nocturnal fat oxidation in response to overfeeding predicts 5-year weight gain in adults. Obesity. 2017 May;25(5):873-880. ***Editorial pick-up***

19.**Bergouignan A,** Legget KT, De Jong N[S], Kealey EA, Groppel JL, Jordan C, O'Day R, Hill JO, Bessesen DH. Effect of frequent interruptions of prolonged sitting on self-perceived levels of energy, mood, food cravings and cognitive function. Int J Behav Nutr Phys Act, 2016. **13**:113. ***Press release.***

20.Gastebois C, Villars C, Drai J, Canet-Soulas E, Blanc S, **Bergouignan A**, Lefai E, Simon C. Effects of training and detraining on plasma adiponectin concentrations and muscle sensitivity in lean and overweight men. Eur J Appl Physiol, 2016 Sep 8

21.**Bergouignan A,** Latouche C, Heywood S, Grace M, Natoli A, Luthoodoo M, Owen N, Dunstan DW, Kingwell BA. Frequent interruption of sedentary time modulates contraction- and insulin-stimulated glucose uptake pathways in skeletal muscle. Sci Report, 2016 Aug 24;6:32044.

22.**Bergouignan A**, Stein P, OGorman D, Blanc S. Towards Human Exploration in Space: The THESEUS review series on nutrition and metabolism research priorities. npg Microgravity, 2016. 2:16029

23.Rudwill F[S]*, **Bergouignan A*,** Gastebois C, Gauquelin-Koch G, Lefai, E, Blanc S, Simon C. Effect of enforced physical inactivity by 60-d of bed rest on hepatic markers of NAFLD in healthy normal-weight women. Liver Int. 2015 Jun;35(6):1700-6.

24.**Bergouignan A**, Kealey E, Jackman MR, Bessesen DH. 24 h total and dietary fat oxidation in lean, obese and reduced-obese adults with and without a bout of exercise. PloS One. 2014 8;9(4):e94181.

25.Simon C, Kellou N, Dugas J, Platat C, Schweitzer B, Hausser F, **Bergouignan A**, Lefai E, Blanc S. A socio-ecological approach promoting physical activity and limiting sedentary behavior in adolescence showed weight benefits maintained 2.5 years after intervention cessation. Int J Obes. 2014 Feb 10.

26.Rudwill F[S]*, Blanc S*, Chouker A, Heer M, Gauquelin-Koch G, Simon C, **Bergouignan A**. Effects of different levels of physical inactivity on plasma visfatin in lean and healthy men. Appl Physiol Nutr Metab, 2013 Jun;38(6):689-93

27.Villars C, **Bergouignan A**, Dugas J, Antoun E, Schoeller DA, Roth H, Blanc S, Simon C. Validity of Acti-heart to measure free living physical activity energy expenditure in young adults. J Appl Physiol, 2013 Feb;114(3):371-9

28.**Bergouignan A***, Momken I*, Antoun E, Platat C, Chery I, Zahariev A, Gabert L, Normand S, Laville M, Lefai E, Vidal H, Simon C, Blanc S. Activity energy expenditure is a major determinant of dietary fat oxidation and trafficking, but the deleterious effect of detraining is more marked than the beneficial effect of training at current recommendations, Am J Clin Nutr, 2013 Sep;98(3):648-58.

29.**Bergouignan A***, Antoun E*, Momken I*, Schoeller DA, Simon C, Blanc S. Effect of contrasted levels of habitual physical activity on metabolic flexibility. J Appl Physiol, 2013 Feb;114(3):371-9,

30.**Bergouignan A**, Gozansky WS, Barry DW, Leitner W, MacLean PS, Hill JO, Draznin B, Melanson EL. Increasing dietary fat elicits similar changes in fat oxidation and markers of muscle oxidative capacity in lean and obese humans. PLoS One. 2012;7(1):e30164

31.**Bergouignan A, Habold C, Normand S, Simon C, Blanc S.** Urinary C-peptide is not a bioindicator of energy balance in humans, Obesity (Silver Spring). 2012 Mar;20(3):683-8

32.**Bergouignan A**, Rudwill F[S], Simon C, Blanc S. Physical inactivity as the culprit of metabolic inflexibility: Evidence from bed-rest studies. J Appl Physiol, 2011 111(4) :1201-10. ***Invited Review***

33.Momken I*, Stevens L*, **Bergouignan A***, Desplanches D, Rudwill F, Chery I, Zahariev A, Zahn S, Stein TP, Sebedio JL, Pujos-Guillot E, Falempin M, Simon C, Coxam V, Andrianjafiniony T, Gauquelin-Koch G, Picquet F, Blanc S. Resveratrol prevents the wasting disorders of mechanical unloading by acting as a physical exercise mimetic in the rat. FASEB J, 2011; 25(10):3646-60. ***F1000, Press release.***

34.MacLean PS, **Bergouignan A**, Cornier MA, Jackman MR. Biology's Response to Dieting: the Impetus for Weight Regain, Am J Physiol Regul Integr Comp Physiol, 2011; Sep;301(3):R581-600.

35.Antoun E*, Momken I*, **Bergouignan A***, Villars C, Platat C, Schoeller DA, Blanc S, Simon C. The [1-13C]acetate recovery factor to correct tracer-derived dietary fat oxidation is lower in overweight insulin-resistant subjects, e-SPEN, Eur e-J Clin Nutr Metab, 2010; 5: e173-179.

36.Melanson EL, Ingebrigtsen JP, **Bergouignan A**, Ohkawara K, Lighton JRB. A new approach for flow-through respirometry measurements in humans, Am J Physiol Regul Integr Comp Physiol. 2010 Jun; 298(6):R1571-9

37.**Bergouignan A**, Momken I, Schoeller DA, Normand S, Zahariev A, Lescure B, Simon C, Blanc S. Regulation of energy balance during long-term physical inactivity induced by bed rest with and without exercise training. J Clin Endocrinol Metab.2010 Mar;95(3):1045-53

38.**Bergouignan A**, Momken I, Schoeller DA, Simon C, Blanc S. Metabolic fate of saturated and mono-unsaturated dietary fats: the Mediterranean diet revisited from epidemiological evidences to cellular mechanisms, Progress Lipid Research, 2009 May-July, 48(3-4):128-47

39.**Bergouignan A**, Trudel G, Simon C, Schoeller DA, Chopard A, Desage M, Burdge GC, Gauquelin-Koch G, Normand S, Blanc S. Enforced physical inactivity differentially alters dietary oleate and palmitate trafficking. Diabetes. 2009, Feb; 58(2): 367-76

40.**Bergouignan A**, Schoeller DA, Votruba S, Simon C, Blanc S. The acetate recovery factor to correct tracer derived dietary fat oxidation in humans. Am J Physiol Endocrinol Metab. 2008 ; 294(4) :E645-53

41.**Bergouignan A**, Schoeller DA, Normand S, Gauquelin-Koch G, Laville M, Shriver T, Desage M, Maho YL, Ohshima H, Gharib C, Blanc S. Effect of Physical Inactivity on the Oxidation of Saturated and Monounsaturated Dietary Fatty Acids: Results of a Randomized Trial. PLoS Clin Trials, 1(5), e Sept 2006

42.**Bergouignan A**, Blanc S. Énergétique de l'obésité. J Soc Biol, 200(1), p.29-35, 2006.

43. Zahariev A, **Bergouignan A**, Caloin M, Normand S, Gauquelin-Koch G, Gharib C, Blanc S. Skinfold Thickness versus Isotope Dilution for Body Fat Assessment during Simulated Microgravity: Results from three Bed-Rest Campaigns in Men and Women with and without Countermeasures. Eur J Appl Physiol, 95(4), p. 344-50, Octobre 2005

- Articles under revision in peer-reviewed journals.

44.Criscuolo F, Sueur C, **Bergouignan A**. Find new perspectives for human deep space exploration: Sitting on the shoulder of evolution. Frontiers in Physiology: Environmental, Aviation & Space Physiology

45.Laurens C[S], **Bergouignan A**, Moro C. Exercise-released myokines in the control of energy balance. Frontiers in Physiology: Exercise physiology

46.Dempsey PC, Matthews CE, Dashti SG, Dohert AR, **Bergouignan A**, van Roekel EH, Dunstan DW, Wareham NJ, Yates TE, Wijndaele TE[#], Lynch BM[#]. Sedentary behaviours and chronic disease: mechanisms and future directions. J Phys Act Health

47. Blanchet L, Fuchs B, Støen OG, **Bergouignan A**, Ordiz A, Arnemo JM, Evans AL. Movement and heart rate in the Scandinavian brown bear (Ursus arctos). Animal Biotelemetry

- **Articles published in non-peer-reviewed congress acts.**

1. Laurens C[S], Blanc S, **Bergouignan A.** The obligatory exercise countermeasure program during space flight: is it time for revision ? COSPAR, 42nd Scientific Assembly, August 2018.

2. **Bergouignan A**, Blanc S. Energy and oxidative balances in response to the space environment. COSPAR, 36th Scientific Assembly, p.102. 16-23, July 2006.

3. Blanc S, **Bergouignan A**. La dépense énergétique : composantes et déterminants. Nutrition & Facteurs de risque, 3, p. 19-22, Janvier 2005

- **Articles published in non-peer-reviewed journals**

1. **Bergouignan A**, Blanc S. La nutrition au centre de la médecine spatiale. Biofutur, 318 :44-46 2011.

2. **Bergouignan A**, Blanc S, Simon C. Calories et sante : Quantité ou qualité. Les Cahiers de La Nutrition, 45(4), p.180-189, Septembre 2010.

3. **Bergouignan A**, Blanc S. Le métabolisme énergétique s'adapte à l'inactivité… Diabète & Obésité, 2(8), p. 106-112, April 2007.

- **Book chapters**

1. **Bergouignan A**, Blanc S. Chapitre Adaptations métaboliques. L'Homme dans l'espace. M.A. Custaud, S. Blanc, G. Gauquelin-Koch, C. Gharib. (Eds) Caméléon Studio, *in press*.

2. Momken I, **Bergouignan A.** Chapitre Les Contremesures**.** L'Homme dans l'espace. M.A. Custaud, S. Blanc, G. Gauquelin-Koch, C. Gharib. (Eds) Caméléon Studio, *in press*.

3. Besessen D, **Bergouignan A.** Chapter 18 : Behavior Change Strategies for Increasing Exercise and Decreasing Sedentary Behaviors in Diabetes. Diabetes and Exercise: From Pathophysiology to Clinical Implementation, Second Edition, Reusch J, Regensteiner J, Stewart KJ, Veves A editors, 2018.

4. Blanc S, **Bergouignan A**, Peyroux C, Nazare JA, Simon C. Chapitre 9: La transition comportementale: Focus sur l'activité physique. Ecologie de la Santé, 1ere edition, Renaud F, Boetsch G, Blanc S, Hossaert M, Collection Institut Ecologie et Environnement, Cherche Midi, 2017.

5. Dunstan DW, Howard BJ, **Bergouignan A**, Kingwell BA, Owen N. Physiological effects of reducing and breaking up sitting time. In W. Zhu & N. Owen (Eds.), *Sedentary behavior and health concepts, assessments, and interventions* (pp. 31-43, 360-361). Champaign, IL: Human Kinetics, 2017.

6. Simon C, **Bergouignan A,** Laville M. Chapitre : Alimentation et Obésité**.** Traité de Médecine et Chirurgie de l'Obésité. Arnaud Basdevant. Flammarion Médecine, 5e édition, Paris, France, 2009.

7. **Bergouignan A**, Blanc S. La nutrition au centre de la médecine spatiale. L'alimentation au fil de la recherche, Fondation Alimentarium, Vevey, p.51-60, March 2009.

11. Grants & Funding

A summary of all the submitted grants and proposals since my PhD defense is given in Annex.

2019 **French Society for Nutrition Award (SFN)**
€20,000 – 1 year – PI
Etudier la transition épidémiologique dans une population pastoraliste nomade pour comprendre l'impact des changements du régime alimentaire et l'activité physique sur la régulation du poids.
CNRS Groupe de Recherche « Sport et Activité Physique » (Research group « Sport and Physical Activity ») Bourse de Thèse
€111,000 – 3 year – PI, Mentor
Fragmenter le temps passé assis : Une nouvelle stratégie d'activité physique au-delà de la pratique d'un sport pour la santé métabolique
French Space Agency (CNES)

€50,000 – 1 year – Co-I
PI- Stéphane Blanc
Functional and metabolic consequences of ectopic fat storage during bed rest: A mechanistic and kinetic approach for testing an anti-oxidant/anti-inflammatory dietary mix as nutrition countermeasure
French Space Agency (CNES)
€20,000 – 1 year – Co-I
PI- Stéphane Blanc
ENERGY: Role of spontaneous physical activity in the regulation of energy balance in the astronauts during long-term space missions
French Space Agency (CNES)
€30,000 – 1 years - PI
Short-term effects of dry immersion on muscle myokines and muscle nutrient metabolism in young healthy males

2018 NIH CCTSI TTOS TL1 pre-doctoral fellowship
$40,000 – 1 year – Mentor
PI – Nathan DeJong
Metabolic effects of breaking up sedentary time
CNRS Mission Interdisciplinaire
€30 000 - 1 year – PI
Testing evolutionary medicine concepts: Is total energy expenditure homeostatically regulated in humans?
CCTSI Junior Co-Pilot Award
$30,000 – 1 year – PI
Effect of frequent interruptions of sedentary time on glucose homeostasis in free-living prediabetic overweight adults

2017 Prix de recherche IDF - FRM pour les sciences de l'alimentation
€40,000 – 2 years – Co-I
PI- Stéphane Blanc
Epidemiological transition in Fulani nomad pastoralists in Senegal: Impact of sedentarization on life style, diet, physical activities and weight.
French Space Agency (CNES)
€50,000 – 1 year - PI
Short-term effects of dry immersion on metabolic flexibility in young healthy males
CNRS National Institute of Ecology and Environment (INEE) Laboratory International Agreement (LIA) between the CNRS IPHC-DEPE UMR7178 Unit and the University of Colorado, Division of Endo, Anschutz Health & Wellness Center
€50,000 – 5 years - PI
ACTIMOVE: The global transition of physical activity: Management of a conflict between environment and health

2016 University of Colorado, Colorado Clinical & Translational Scientific Institute Microgrant
€20,000 - 2 years - PI
Effects of microbouts of activity on metabolic health.
Colorado School of Public Health, The Mountains and Plains Education and Research Center (MAP ERC), Occupational & Environmental Health & Safety award
$15,000 – 2 years - PI
Microbouts of activity to combat sitting disease in office workers
CNRS INEE PEPS Blanc Project (Pilot funding for Exploratory Projects)
€15,000 – 1 year - PI
What do the brown bear and European hamster are dreaming about? Study of the role of arousal episodes during hibernation

2015 University of Colorado, School of Medicine, K-awardee Grant
$25,000 – 1 year

2014 University of Colorado, Colorado Clinical & Translational Scientific Institute Microgrant
$20,000 - 2 years - PI
Breaking-up prolonged sitting to offset sedentary behaviors-induced metabolic alterations.

National Institute for Health / National Institute of Diabetes and Digestive and Kidney Diseases (NIH/NIDDK) K99/R00 Pathway to the Independence Award $925,000 - 5 years - PI
Breaking-up prolonged sitting to offset sedentary behaviors-induced metabolic alterations.

2013 Australian Government Endeavour Postgraduate Research Fellowship
$25,000 - 6 months
Effect of frequent breaks-up of prolonged sitting on metabolic flexibility.

2012 National Obesity Research Center (NORC) Young Investigator Award Extension
$10,000 - 1 year - PI
Mechanistic approach of dietary fat partitioning in muscle and liver in Zucker lean, obese and reduced-obese rats.

2011 Colorado Clinical & Translational Science Institute Mentored Pilot Study Award
$20,000 - 1 year - PI
A novel tracer method to understand the mechanisms of reduced dietary fat oxidation in obese and reduced-obese humans.
NORC Young Investigator Award
$20,000 - 1 year - PI
Dietary fat oxidation and trafficking in obesity and reduced-obesity.

2004 French Space Agency (CNES) Graduate Fellowship
Effect of physical exercise on energy metabolism and metabolic fate of dietary fatty acids in women in simulated microgravity (WISE2005 Study).
French Ministry of Education and Research Graduate Fellowship (declined)
CNRS Graduate Fellowship (declined)

2003 Louis Pasteur University, Graduate Scholarship, Strasbourg, France.

12. Formal trainings & career development

2018 NORC Calorimetry Workshop, University of Colorado, Denver, CO, USA
CCTSI Co-Mentor Program, University of Colorado, Denver, CO, USA
CCTSI JUMP (Junior Faculty Mentor) Program, University of Colorado, Denver, CO

2014 NIH/NIDDK K-awardees workshop for Career Development, Bethesda, DC, USA.
CCTSI Biostatistics Short Course (16h), UC, Denver.
Scientific and Technical Writing Workshop, CU Denver, Graduate School BEST Program, University of Colorado
Team Building and Leadership Development Workshop. CU Denver, Graduate School BEST Program, University of Colorado.
Training in Responsible Conduct of Research, University of Colorado.
Lab Management Workshop, CCTSI, University of Colorado.

2012 Isotopic Tracers in Metabolic Research Courses, (3 days), Little Rock, Arkansas.
Career Development and Reaching Independence Workshop, The Endo Society, Houston, TX, USA

13. Professional memberships

2019- The Obesity Society
American Physiology Society

2018- Sedentary Behavior Research Network

16- American College of Sports Medicine

2014 American Physiology Society
The Endo Society

14. Local, national and international collaborations

Vincent VIBLANC	CNRS-IPHC UMR7178, Strasbourg France
Cédric SUEUR	CNRS-IPHC UMR7178, Strasbourg France
Fabrice BERTILE	CNRS-IPHC UMR7178, Strasbourg France
Chantal SIMON	CRNH, Lyon, France
Etienne LEFAI	UNH, INRA, Clermont-Ferrand France
Enguerran MACIA	CNRS UMI 3189, Marseille France
Priscilla DUBOZ	CNRS UMI 3189, Marseille France

Basile CHAIX	INSERM iPLesp UMR S 1136, Paris France
Cédric MORO	INSERM I2MC, Toulouse France
Angèle CHOPARD	Université of Montpellier France
Donal O' GORMAN	Dublin City University, Dublin Ireland
Daniel BESSESEN	Division of Endocrinology, University of Colorado, Denver, CO, USA
Paul MACLEAN	Division of Endocrinology, University of Colorado, Denver, CO, USA
Edward L. MELANSON	Division of Endocrinology & Division of Geriatrics, University of Colorado, Denver, CO, USA
Michael RUDOLPH	Division of Endocrinology, University of Colorado, Denver, CO, USA
Matthew JACKMAN	Division of Endocrinology, University of Colorado, Denver, CO, USA
Corey RYNDERS	Division of Geriatrics, University of Colorado, Denver, CO, USA
Kristen BOYLE	Department of Pediatrics, University of Colorado, Denver, CO, USA
Josiane BROUSSARD	Department of Health & Exercise Sciences, Colorado State University, Fort Collins, CO, USA
David DUNSTAN	Baker IDI Heart & Diabetes, Melbourne, Australia
Neville OWEN	Baker IDI Heart & Diabetes, Melbourne, Australia

LIST OF ABBREVIATIONS

ACLS1
AEE, Activity energy expenditure
AIRg, Acute insulin response to glucose
ANR, Agence National pour la Recherche (French National Agency for Research)
BDC, Baseline data control
BIS, Bio-impedance spectroscopy
BMI, body mass index
CCTSI, Colorado Clinical & Translational Scientific Institute
CD36, fatty acid transporter CD36
CGMS, constant glucose monitoring system
CPT1, Carnitine palmitoyl transferase 1
CTRC, Clinical & Translational Research Center
CNES, Centre National des Etudes Spatiales (French Space Agency)
CRNH, Centre National de Recherche en Nutrition Humaine, (National Center for Human Nutrition)
DIT, diet-induced thermogenesis
DLR, German Space Agency
DLW, doubly labelled water
DEPE, Department of Ecology, Physiology and Ethology
DI, disposition index
ERC, European Research Council
ESA, European Space Agency
FABPpm, fatty acid binding protein of the plasma membrane
FATP1, fatty acid transport protein 1
HbA1c, glycated hemoglobin
INSERM, Institut National de Santé et Recherche Médicale (French National Institute of Health and Medical research)
IPHC, Institut Pluridisciplinaire Hubert Curien
IVGTT, intravenous glucose tolerance test
LDL, Light density lipoprotein
LIA, Laboratoire Interntaional Associé (Joint International Lab)
LIPOX, lipid oxidation study
MICRO, microbouts of activity, less or equal to 5 minutes
MVPA, moderate-to-vigorous physical activity
npRQ, non-protein respiratory quotient
NIH, National Institute for Health
NIDDK, National Institute for Ingestive Diseases, Diabetes and Kidney
OECD, Organisation for Economic Co-operation and Development
OGTT, oral glucose tolerance test
ONE, One long continuous bout of activity
PAGRAS, Physiological Adaptations to GRAvity & Health
PRA, Personal research assistant
RMR, resting metabolic rate
RQ, respiratory quotient
SFN, Société Française de Nutrition (French Society for Nutrition)
SI, Insulin sensitivity
T2D, type 2 diabetes
TEE: Total energy expenditure
WHO, World Health Organization

15. The etiology of the chronic diseases under the prism of evolution

The global epidemic of obesity and chronic diseases results from the confrontation between a "normal" physiology resulting from natural selection and a patho-environment. The last century has seen our environment evolved from a "traditional" to a "Western" lifestyle. The "traditional" environment, characterized by relatively scarce food and high energy expenditure, has promoted so-called "leptogenic" behaviours and a variability in the average body mass index (BMI) dependent on individual genetic predisposition to normal weight gain (left-hand side, Figure 1). Our modern "social" and "built" environment has led to the emergence of obesogenic behaviours encouraged by an abundance of low-cost, high-density, high-fat food and low demand for physical activity (right-hand side, Figure 1). Although the variability of BMI obviously depends on individual genetic predisposition, this new environment favours the expression of an obese phenotype through an overall positive energy balance. Our societies have therefore built an ecological niche in which junk food and sedentary lifestyles are the new standards of living. While this mutation is considered an improvement in living conditions, it has created a gap between the evolutionary history and the current human environment, which has resulted in an increased prevalence of many chronic non-communicable diseases and a reduction in life expectancy at birth for the first time in US history [1, 2].

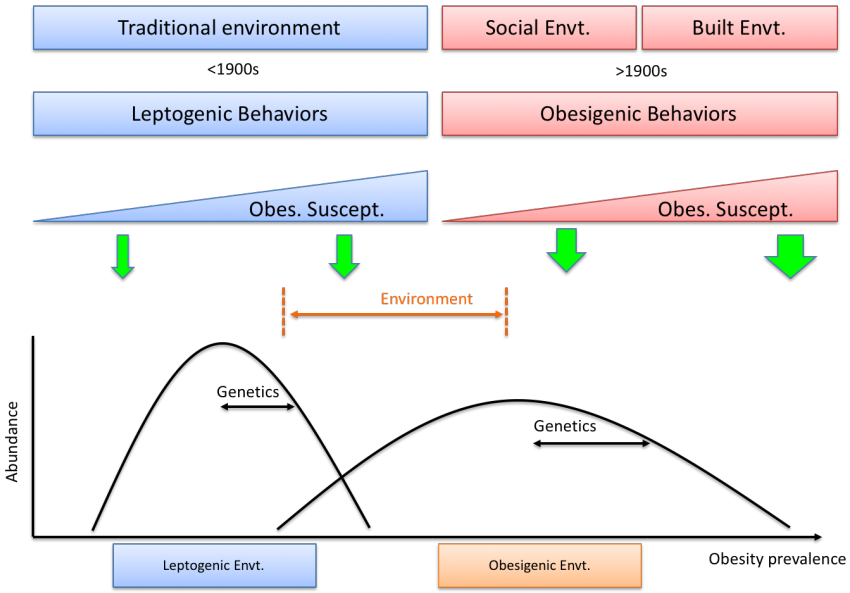

Figure 1: Gene-environment interaction on the individual risk to develop obesity. Based on [3].

Decades of research have unfortunately failed to prevent the continuous rise of chronic diseases prevalence. Understanding modern health problems cannot be achieved without an evolutionary and ecological approach. The evolutionary approach recognizes the biological constraints imposed by the fact that most of human evolution took place when our ancestors were hunter-gatherers. Indeed, 95% of human biology, and probably human behavior, was naturally selected at the time of the emergence of the modern human genome with the appearance of Homo sapiens about 200,000 years ago [4]. Since then, our genetic heritage, although in constant evolution, has undergone few mutations and has remained relatively stable in terms of our physiology. Although genes play a role in regulating human metabolism through individual susceptibility, they alone cannot explain the recent evolution of chronic diseases, including obesity, insulin resistance, type 2 diabetes, atherosclerosis, cardiovascular and coronary heart disease, hypertension, stroke, dyslipidemia, non-alcoholic fatty liver disease, cancers, etc., whose prevalence is increasing.

The ecological approach recognizes the importance of environmental factors in the onset of modern diseases. Environmental factors that differ from those of our ancestors are specifically related to our lifestyles, including eating and movement behaviors (physical activity). Western populations or populations that have completed their epidemiological transition, i.e. the change in the pattern of mortality and disease from high children mortality and infectious diseases to chronic diseases, have largely adopted sedentary behaviors and are mainly inactive.

16. The physical activity transition

The evolutionary history of mankind largely took place before the emergence of agriculture (3-4 million years ago), while advances in agriculture and technology occurred on a relatively short time scale of about 10,000 years. Before agriculture, humans subsisted on fodder and hunting for nutrient-rich but hard-to-reach food. These activities required moderate to high intensity physical activity. During the Holocene, a transition from fodder to agriculture began, which was accompanied by an increase in physical activity until 200 years ago when the Industrial Revolution began. It began in Great Britain at the end of the 18th, early 19th century and gradually spread to the United States and other parts of Europe. It has produced major technological, socio-economic and cultural changes that have led to the replacement of a labor-based economy by an economy based on industry and mechanized manufacturing, allowing easy access to food with minimal energy demand.

This revolution has led to significant changes in physical activity due to a reduction in professional environments requiring high energy expenditure such as mines, forests or farms in favor of sedentary environments with very low levels of physical activity. While the majority (60-70%) of workers in OECD countries had manual (blue collar) jobs in the 1970s, from the 1990s onwards, about 60-70% of workers had jobs in an office (white-collar) [5]. The expansion of the tertiary sector has reduced physical activity at the workplace by 20% since 1960 and a 35% reduction is likely to be achieved by 2030 [5]. Changes in physical activity behavior have spread to all spheres of daily life: professional (office) or domestic life (washing machines, washing machines, etc.), transport (car) and leisure (video games, Internet, television). All this has greatly reduced the need for physical activity in everyday life. These changes have been accompanied with major health, socio-economic and environmental consequences.

17. Consequences of physical inactivity

Globally more than a quarter of adults (1.4 billion) were not getting enough physical activity in 2016 (44). Lack of physical activity is now considered a key risk factor for many chronic diseases. Physical inactivity is the 2nd current cause of death in the United States and the 4th worldwide [6]. In Europe, it causes the premature death of 600,000 people per year, or 10% of total mortality [7]. The Lancet's 2012 series on physical inactivity presents compelling evidence on the burden of chronic diseases attributable to physical inactivity - type 2 diabetes (7%), coronary heart disease (6%), breast cancer (10%) and colon cancer (10%) [6]. Physical inactivity has a high economic cost on all health systems worldwide that has been estimated at INT$53.8 billion worldwide and may even be higher [8]. Physical inactivity was then recognized as a major public health problem by the World Health Organization (WHO) and The Lancet in July 2012 in which it was written: "Due to its prevalence, wide geographical distribution and health effects, physical inactivity must be recognized as a pandemic with significant health, environmental, societal and economic consequences". This statement was reiterated and reinforced in a new special issue of the Lancet in July 2016 [9]. The Lancet's 2016 Series encourages government policies to take physical activity more seriously, to include recommendations on reducing sedentary time in physical activity recommendations, and to provide the necessary funding and resources to implement national policies [9]. Without a rapid action effort, WHO's goal of reducing the prevalence of physical inactivity by 10% by 2025 worldwide will not be achieved. A body of experimental evidence is needed to develop future public health recommendations on physical activity and minimum sedentary time.

18. Sedentary behaviors, an independent component of the physical activity and health equation

While the prevalence of physical inactivity (i.e. not meeting current recommendations) has not been reduced over the past 10 y, time spent in sedentary behaviors has increased from 5.7 h/d to 6.4 h/d from 2007 to 2016 [10]. Sedentary behaviors are defined as daily-living and occupational tasks that are associated with low energy expenditure (~1kcal/min) performed in a seated, lying or in reclined position [11]. Epidemiologic studies have identified positive associations between the time spent sedentary and early mortality, and the risk of developing obesity, type 2 diabetes (T2D), and cardiovascular diseases [12]. These associations have been reported for all age, sex, and ethnicity, are independent of adiposity and exist even when the level of recommended physical activity is reached [13]. This suggests that spending too much time sitting is different from not doing enough exercise. Research to understand the sedentary behaviors physiology are needed as well as the development of strategies that aim to offset their adverse health effects.

Note: References in blue font are articles stemming from my own research.

In this general context, the overall objectives of my research program are to **(i)** understand the role of physical inactivity and sedentary behaviors in the emergence of metabolic diseases, including obesity, insulin resistance and T2D, **(ii)** develop innovative strategies that can offset the deleterious effects of physical inactivity and sedentary behaviors.

My scientific approach combines unique models and paradigms set in extreme environments and in real life to understand the physiopathology of sedentary behaviors and physical inactivity. Using extreme environments, I expect to characterize underlying mechanisms. Studies conducted in the real life aim to confirm or not results observed in extreme conditions. For these studies I employ a sophisticated approach of integrative physiology studying the metabolic responses to different levels of activity from the whole-body level to the organ, cell, protein and gene levels. My research specifically aims to ❶ determine the effects of sedentary behaviors on key parameters involved in the regulation of body weight and metabolic health, ❷ including metabolic flexibility which is defined as the ability to adjust substrates use to changes in substrate availability and demand and considered a core component of metabolic health, ❸ test the efficacy of new strategies (diet or physical activity/exercise) in the prevention of the adverse metabolic health outcomes, ❹ understand how the different components of energy balance , i.e. the result between energy input and output, interact between each other and regulate body weight, and ❺ by adopting a socio-eco-physiological approach, understand the respective role of biological, environmental, sociological and anthropological (lifestyle/culture) factors of the regulation of body weight and metabolic health. The ultimate goal of this research program is to translate findings obtained in rigorous and scientifically robust studies into guidelines of public health to improve human condition.
My research program is summarized in Figure 2. Each question is addressed in this order in the text below.

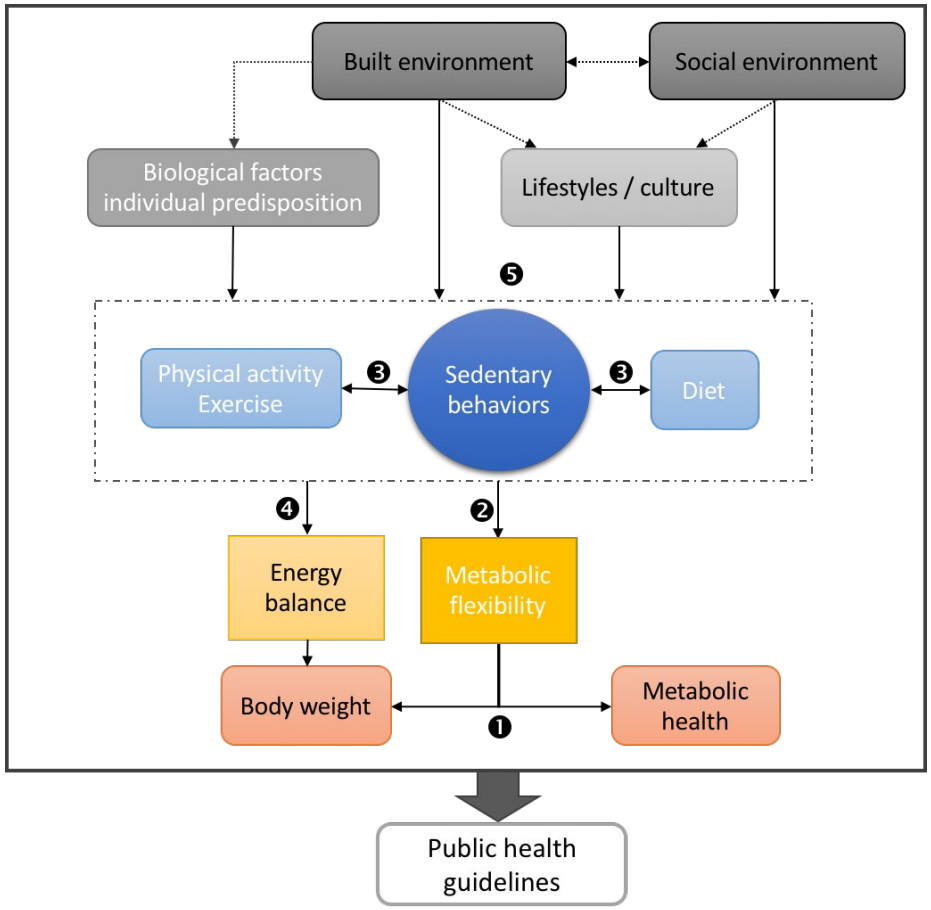

Figure 2 : Summary of the research program. Dotted arrows are associations or cause-to-effect relationships that are important but are not studied in the present project.

19. What are the health consequences of sedentary behaviors and physical inactivity?

19.1. Physical inactivity triggers metabolic features close to those observed in adults with obesity and type 2 diabetes

This axis has been one of my main areas of research since I have started my PhD Thesis, i.e. for the last 15 years. Specifically, I have been studying human energy and metabolic adaptations to physical inactivity. To experimentally study the direct effects of physical inactivity on the body in humans is challenging. To do so, I use unique paradigms employed in space research, that mimic the effects of weightlessness on Earth, ie. bed rest (Photo 1) [14] and more recently dry immersion (Photo 2) models. Because microgravity leads to hypokinesia and hypodynamia, the simulation of its effects on Earth provides us with original information on the effects of physical inactivity.

PHOTO 1: Bed rest model

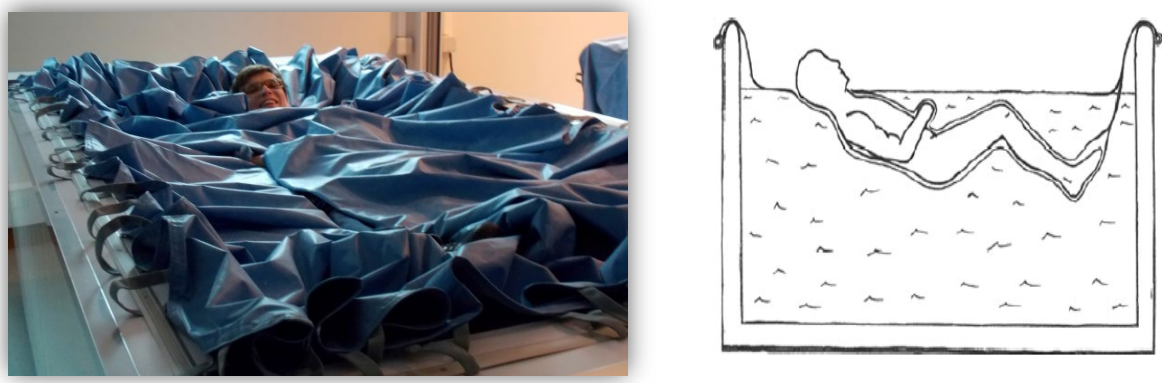

PHOTO 2 : Dry immersion model

Combining data from bed rest studies obtained over the last 15 years, I showed in healthy men and women that physical inactivity per se, independent of detectable changes in energy balance [15], increases plasma proinflammatory biomarkers, triggers the development of insulin resistance, and alters post-prandial nutrient metabolism [16-21]. These studies mainly correspond to the research I undertook during my PhD Thesis under the mentorship of Stéphane Blanc and Chantal Simon, and the PhD Thesis of a graduate student I co-mentored (F Rudwill). They were conducted in collaboration with the lab of Angèle Chopard (University of Montpellier) and of Dominique Langin (I2MC Toulouse); results are summarized in figure 3.

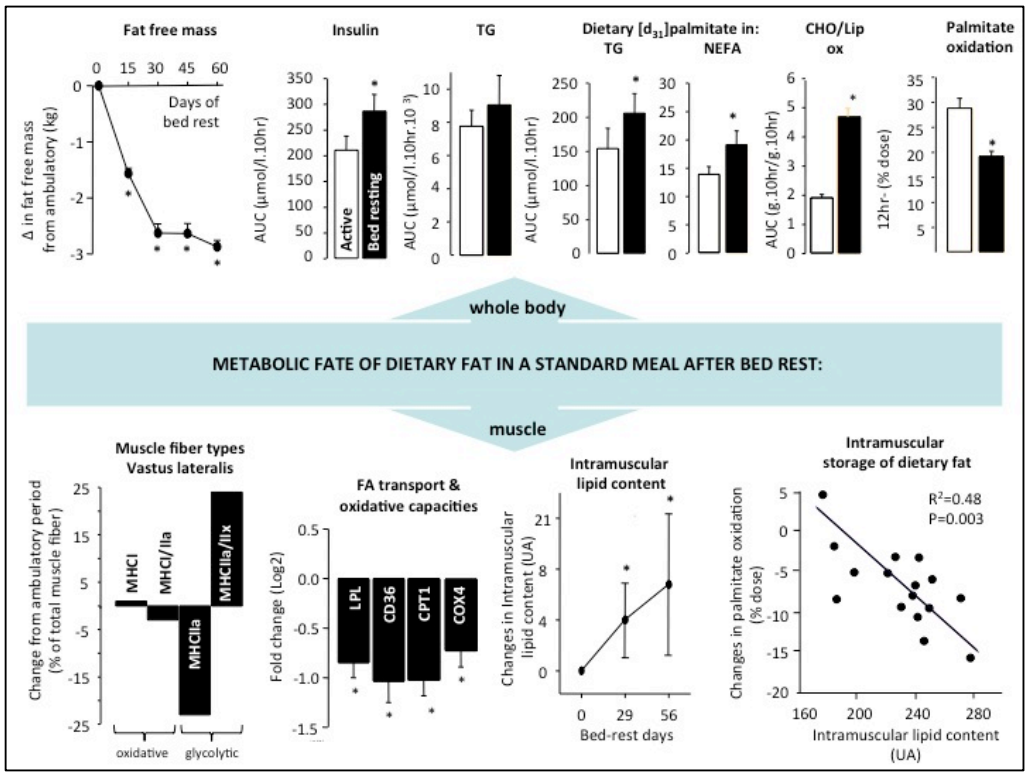

Figure 3 : Summary of metabolic responses to bed-rest induced inactivity in healthy and lean male and female adults

19.2. Physical activity predicts dietary fat oxidation, a key parameter of body weight regulation

These results were subsequently confirmed for levels of physical inactivity closer to what is observed in the general population. By studying the ability to oxidize exogenous lipids in 1) trained subjects subjected to one month of inactivity and 2) sedentary subjects of normal weight subjected to two months of training according to current recommendations, we unexpectedly observed a strong positive relationship between changes in energy expenditure related to physical activity (AEE) and changes in the ability to oxidize dietary fat for both saturated (palmitate) and monounsaturated (oleate; **Figure 4**) fatty acids [22]. A complementary mechanistic approach suggested that this relationship was directly related to muscle-level modulation of gene expression of plasma membrane and mitochondria transporters (FABPpm, CD36, FATP1, CPT1) and enzymes responsible for acyl-CoA fatty acid activation (ACSL1) [22]. Again, the effects of changes in physical activity were observed independently of changes in the energy balance. These studies were led by Stéphane Blanc and Chantal Simon in close collaboration with Etienne Lefai of the CRNH Lyon. I served as a Co-I.

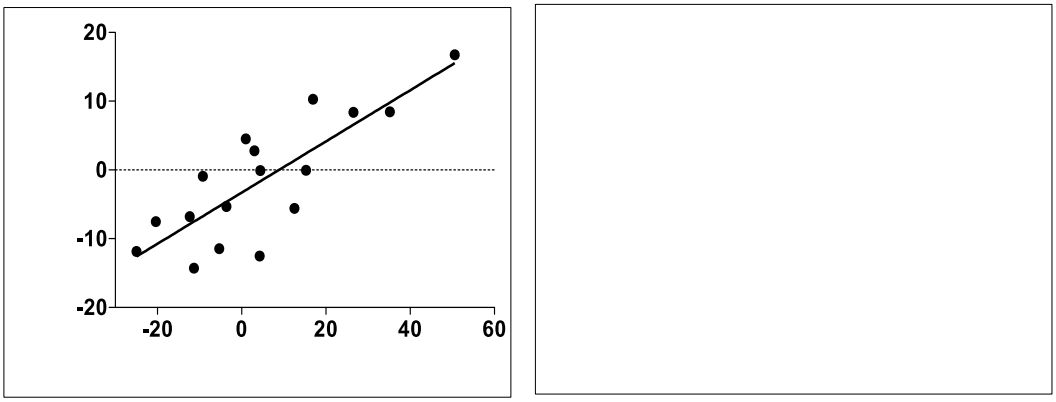

Figure 4 : Relationship between changes in dietary palmitic (left) and oleic (right) fatty acid oxidation and activity energy expenditure (AEE) in response to longitudinal changes in physical activity, i.e. 2-months aerobic exercise training and 1-month detraining in sedentary and physically active normal-weight male adults, respectively.

Based on these available findings, I have developed in 2011 a hypothesis that describes the cascade of events triggered by physical inactivity (Figure 5) and that was published in an invited review in a special issue on physical

inactivity physiopathology of the Journal of Applied Physiology [16]. It proposes that the three main organs involved in energy homeostasis, i.e. liver, muscle and adipose tissue, are affected in a concerted manner in response to physical inactivity to achieve a metabolic state similar to that described in overweight, diabetic and metabolic syndrome subjects. The goal of my future research will be to test this overall hypothesis.

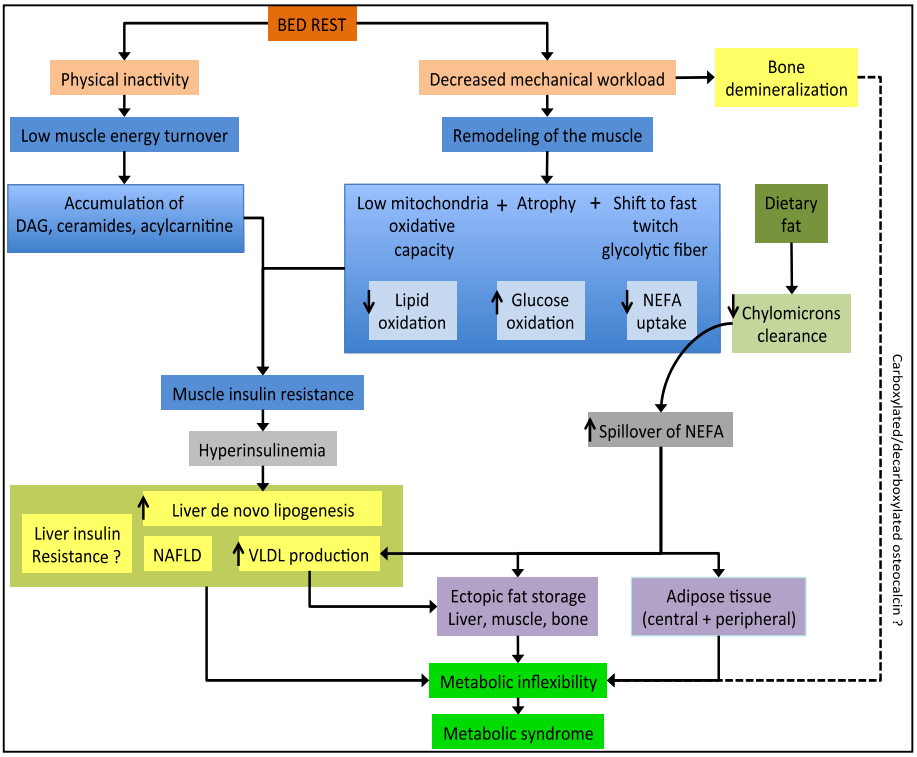

Figure 5: Central hypothesis of the cascade of events triggering the development of metabolic diseases (metabolic syndrome) under physical inactivity conditions

20. Is metabolic flexibility a central component of the health – physical activity relationship?

20.1. Metabolic flexibility: Definition, concept, methods

In this hypothesis [16], metabolic flexibility is a central component of the cascade of events triggered by physical inactivity. Kelley and Mandarino originally defined the term metabolic flexibility as "the capacity for an organism to adapt fuel oxidation to fuel availability" [23]. The most common experimental approach used to assess metabolic flexibility involves measuring the change in the respiratory quotient (ΔRQ; indirect calorimetry) during a euglycemic-hyperinsulinemic clamp. An increase in RQ under insulin stimulated conditions reflects the suppression of lipid oxidation and greater utilization of glucose for oxidation and storage. Using the clamp method, metabolic flexibility to glucose has been shown to be reduced in a number of clinical conditions and physiological states, including type 2 diabetes, obesity, and aging [23]. The physiologic mechanisms that explain impairments in metabolic flexibility are multifactorial, but appear to be due to reduced skeletal muscle glucose disposal rate [3, 24-26]; impaired suppression of adipose tissue lipolysis [26-29]; reduced suppression of hepatic glucose output [26]; and/or skeletal muscle mitochondrial dysfunction [30, 31]. Collectively, impaired glucose transport, lower fatty acid turnover, and reduced oxidative capacity favor the accumulation of ectopic lipid and multi-organ metabolic dysfunction.

The underlying mechanisms and factors triggering the onset of metabolic inflexibility are not fully elucidated, potentially because the definition of metabolic flexibility is still in debate in the scientific community. For many years, researchers studied the pathophysiology of obesity and related metabolic diseases by focusing on the main metabolic pathways involved in the regulation of metabolism at different levels of integration. These studies have included measures of glucose uptake by peripheral organs, glycolysis, glycogen synthesis in skeletal muscle and liver, mitochondrial fat uptake and oxidation, whole-body and skeletal muscle fat oxidation in different metabolic situations (e.g., fasting, postprandial conditions, exercise, beta-adrenergic stimulation). To understand the independent role of each pathway in the aetiology and development of metabolic diseases, scientists have used different paradigms to create highly controlled metabolic conditions to isolate one pathway or another. While informative, these studies provide a limited view of the holistic

regulation of metabolism. The regulation of energy and fuel homeostasis are intrinsically intertwined and require the integration of a multitude of extrinsic and intrinsic metabolic regulators and effectors. In this line, the concept of metabolic flexibility is powerful as it represents a framework within which changes in fuel oxidation can be examined along with changes in fuel availability that result from modifications in dietary intake, energy demand, or peripheral metabolic processes. It thus represents an integrated assessment of the interaction between environmental factors (diet, physical activity, others) and regulation of the metabolism (organism). Understanding the interaction between environmental and biological factors in the development of metabolic flexibility is important to improve our understanding of the aetiology and progression of metabolic diseases.

In their comprehensive review of metabolic flexibility and insulin resistance, Galgani, Moro (32) suggested that a number of additional metabolic challenges (besides the clamp) should also be considered in the assessment of metabolic flexibility. For example, the switch from glucose to lipid oxidation during an overnight fast (i.e., metabolic flexibility to fasting) or fuel shifts in response to dietary challenges varying in macronutrient composition (e.g., high-fat and high carbohydrate diets) could be considered in the context of metabolic flexibility. I ascribe to the view that any response of fuel metabolism to a stress or challenge, be it environmental or physiological, might provide information about metabolic flexibility. In my view, any paradigm which aims to assess metabolic flexibility must have three components: a *stressor*, a *regulator*, and an *effector*. It is the allostatic relationship between the *regulator* and *effector* in response to *stressor* that is measured experimentally and informs on metabolic flexibility. For example, under the original definition of Kelley and Mandarino (23), the conditions of the clamp serve as the metabolic stressor, and the allosteric relationship between the insulin infusion rate (*regulator*) and ΔRQ (*effector*) provides information on metabolic flexibility. Within this construct, the artificial hyperinsulinemic condition of the clamp is just one challenge to the system, and an important one, but other stressors and challenges, like exercise, fasting, meals, catecholamines infusion, etc., can also be used to examine the response of an effector to a regulator providing new insights into metabolic dysregulation. I believe that the stressor-regulator-effector model of metabolic flexibility will ultimately lead to new insights into integrative pathophysiology of obesity and diabetes. This novel approach of metabolic flexibility was recently published in an invited review [33].

In summary, I believe that it is important for the scientific community to consider a broader definition of metabolic flexibility that includes a variety of potential metabolic and physiologic challenges/stressors that could result in perturbations in the fine tuning between metabolic regulator and effector, which ultimately impact fuel homeostasis. It is within this framework that I have studied metabolic flexibility.

20.2. Do sedentary behaviors trigger metabolic flexibility?

Employing this novel approach, I showed that while exercise training and high levels of daily physical activity improve metabolic flexibility, physical inactivity and sedentary behaviours trigger varying states of metabolic inflexibility [34]. In a 21-day bed rest study, we recently showed that this metabolic inflexible status precedes the development of glucose intolerance in the pathogenesis of insulin resistance in healthy, but physically inactive, adults [35]. In a recent bed rest study completed in December 2017, we further showed that metabolic inflexibility was already developed after 9 days of bed rest (unpublished data).

These results were obtained during a training/detraining study conducted in free-living adult males and four independent long-term bed rest studies, three conducted at the Space Clinic (MEDES, 3-month bed rest in 2001-2002, 2-month bed rest in 2005 (PhD Thesis), 2-mo bed rest in 2017) at the Rangueil Hospital in Toulouse and one at the German Space Agency (DLR, 3 weeks bed rest in 2010-2011) in Cologne, Germany. I have co-mentored the PhD students who conducted the third one (F Rudwill) and the fourth one (A Damiot). These research projects were conducted by our team at the CNRS-IPHC and in close collaboration with Chantal Simon (CRNH Lyon), Donal O' Gorman (Dublin City University), and François Crampes (I2CM INSERM Toulouse). The four bed rest studies were funded by the French Space Agency (CNES). I was co-investigator for the two last ones.

In addition to their effects on metabolic health, sedentary behaviors and metabolic flexibility seem to play a key role in the regulation of body weight. Indeed, we recently showed at the University of Colorado with Daniel Bessesen, Corey Rynders and others that increased sedentary behaviors in the days following a period of overfeeding, like we often have during holidays, as well as metabolic inflexbility in response to acute overfeeding are predicting long-term weight and fat mass gain [36-38].

Mechanisms underlying the development of metabolic inflexible status triggered by physical inactivity have been further investigated during a 5-day dry immersion study that was completed in March 2019. Initial results indicate that dry immersion-induced inactivity rapidly leads to the development of metabolic inflexibility, glucose intolerance and insulin

resistance at the whole-body level. This is accompanied by an alteration in metabolic flexibility in primary myoblasts cultured from fresh muscle biopsies, which may be due to a reduction in the oxidative capacity of the muscles (unpublished data). These data suggest that intrinsic alterations in skeletal muscle cells may be responsible for the development of inactivity induced whole-body metabolic disorders. This work has been conducted by a post-doctorate fellow (C Laurens) I mentor, thanks to funding I received from the CNES (PI), and in collaboration with the I2MC INSERM lab (Toulouse) co-directed by Cédric Moro. Over the next months, we will further investigate the regulation of the lipid and carbohydrate metabolism pathways at muscle level using the muscle biopsies.

Beyond improving our understanding of the physiopathology of physical inactivity, the study of the mechanisms underlying these adverse health effects can be leveraged to develop efficient treatment and preventative strategies.

21. Can the adverse health effects of physical inactivity be off-set?

21.1. Can diet off-set the physical inactivity induced metabolic alterations?

The question of using diet as a strategy to prevent the adverse health effects induced by bed-rest has been addressed during two separate long-term bed rest studies.

21.1.1. The effect of high protein diet

Whey protein has been shown to stimulate protein synthesis during bed-rest [39, 40], prevent hyperinsulinemia [41], increase plasma lipids [42] and ectopic storage in the liver [43] as well as improving insulin sensitivity in older ambulatory adults [44]. We therefore tested whether a supplementation with whey protein during bed-rest could offset the decrement in fat-free mass and metabolic flexibility in the 2010-2011 21-d bed rest conducted in Cologne, Germany. Overall, the whey protein supplementation did not prevent the adverse metabolic adaptations to bed-rest [35].

21.1.2. The effect of a dietary supplementation rich in anti-oxidant and anti-inflammatory components

In the 2-month bed-rest conducted in 2017 at the MEDES in Toulouse, a dietary cocktail enriched in components with anti-oxidative and anti-inflammatory properties was tested. The rationale was based on recent studies suggesting that bioactive nutrients such as polyphenols, vitamins and essential fatty acids may mitigate some metabolic features of physical inactivity. A large body of data exists in humans, rodents and primates demonstrating the effect of polyphenols such as quercetin, resveratrol, cinnamon, grape or green tea extracts on insulin sensitivity, lipid metabolism, inflammation and oxidative stress [45-52]. Imam Momken (post-doctorate fellow at the CNRS IPHC at that time), Laurence Stevens and I also demonstrated in rodents that resveratrol, a polyphenol found in the grapes skin, acts as an exercise mimetic and prevents the deleterious effects of muscle disuse, loss of muscle mass and strength, hyperlipidemia, insulin resistance and decreased lipid oxidation [53]. Based on these promising results, we proposed to test the effects of a cocktail composed of polyphenols, omega-3 fatty acids, vitamin E and selenium to prevent the expected metabolic alterations induced by physical inactivity and sedentary behaviors. This study was undertaken in two steps: a pilot study followed by the more definitive 2-mo bed rest study.

In a 20-d cross-over randomized study, physically active young male adults were asked to reduce their daily steps from approximately 10,000 to 2,000 and ingest a high-fructose diet over the last 10 days of the study to worsen their metabolism. We showed that while the cocktail did not prevent the decrease in insulin sensitivity and its muscular correlates induced by the intervention, it fully prevented the hypertriglyceridemia, the drop in fasting HDL and total fat oxidation, and the increase in *de novo* lipogenesis [54]. The cocktail further prevented the decrease in type-IIa muscle fiber cross-sectional area and was associated with lower protein ubiquitination content. The circulating anti-oxidant capacity was improved by the cocktail following the oral glucose tolerance test (OGTT) [54]. Based on the promising results of this feasibility study in humans, we embarked on the 2-mo bed rest study that was completed in 2017. First results are showing that the cocktail supplementation did not protect against ectopic fat storage or muscle atrophy but prevented at least partially from short- (9 days) and long-term (49 days) metabolic inflexibility, hyper-triglyceridemia and oxidative stress induced by the bed rest (unpublished data).

The feasibility study and the 2-mo bed rest study corresponded to a PhD Thesis I co-supervised (A. Damiot). I was co-investigator on these two studies that were funded by the CNES.

In conclusion, this supplementation can be interesting, especially for people who are unable to practice physical activity such as, bed-bound patients, elderly, or astronauts who are subjected to muscle disuse and very low levels of physical activity. Further advantages are that it is easy to implement, not time-consuming and likely cost-effective. However, it does not counteract all physiological adaptations to physical inactivity and a combination of this diet with other strategies such as exercise should be tested in the future.

21.2. Can exercise offset the adverse metabolic health consequences of sedentary behaviors and physical inactivity?

During my PhD Thesis we tested the effect of a resistive exercise training and a combined resistive and aerobic exercise training to counteract the metabolic alterations induced by bed rest. Surprisingly, in bed rested healthy subjects, the performance of even very large volumes of resistance and aerobic exercise that significantly increased total energy expenditure (**TEE**) did not improve metabolic flexibility and insulin sensitivity [17, 18]. These results indicate that when levels of sedentariness are very high, large volumes of moderate-to-vigorous physical activity (**MVPA**) are not sufficient to improve metabolic health. This supports the message that being too sedentary is different from not doing enough exercise. To my knowledge, these are one of the few evidences supporting an independent effect of sedentary behaviors in the health – physical activity equation.

In the LIPOX study conducted in Strasbourg, the effect of 2-month aerobic exercise training prescribed according to the 2008 physical activity recommendations on dietary fatty acid metabolic fate and TEE was compared in normal-weight and overweight/obese sedentary male adults. We showed that contrary to lean subjects, TEE and activity energy expenditure (**AEE**) did not increase in overweight participants due to a spontaneous decrease in non-training AEE (**Figure 6**). Despite this compensatory behavior, aerobic fitness, insulin sensitivity and fat oxidation (**Figure 6**) were improved by exercise training [55]. The latter was not explained by changes in dietary fat trafficking but more likely by a coordinated response at the muscle level enhancing fat uptake, acylation and oxidation. Independent of energy balance and TEE, exercise training at current recommendations improved fitness and fat oxidation in overweight adults. However, the improved metabolic phenotype of overweight adults was not as healthy as the one of their lean counterparts before the 2-month training, likely due to the spontaneous reduction in non-training AEE.

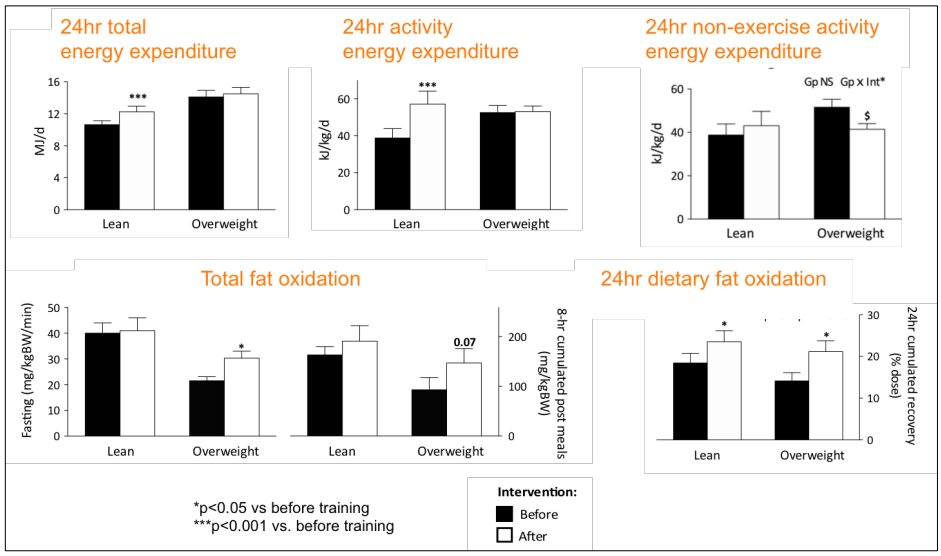

Figure 6. 24h total, activity and non-activity energy expenditure, and 24h total and dietary fatty acid oxidation before and after 2 months of aerobic exercise training in normal weight (n=11) and overweight (n=10) adults

The maintenance of the metabolic differences between normal weight and overweight adults after the 2 months of aerobic exercise training is interesting given that both normal weight and overweight adults have the same ability to adapt to acute exercise. Indeed in a separate study during my post-doctorate fellowship under the mentorship of Daniel Bessesen, I showed that aerobic exercise acutely increases 24h total and dietary fat oxidation in a similar extent in normal-weight and overweight adults [56]. However, when considering adults who had lost weight and maintained weight loss for more than 6 months, those who had combined their diet with an exercise training had metabolic profiles close to those observed in the normal-weight healthy controls [56]. This suggest that both weight loss and regular exercise are needed to reach healthy metabolic profiles. However, weight loss does not seem to be maintainable in absence of high levels of activity. In the context of a collaboration with Vicki Catennacci, Ed Melanson and others at the University of Colorado, we indeed showed that people who successfully maintain weight loss over the long term are individuals who are engaged in very high levels of physical activity, which allows them to maintain high levels of AEE and TEE and thus to likely remain in energy balance at a reduced body weight, and thus avoid body weight gain [57].

Other strategies have been recently proposed to improve metabolic health independent of weight loss.

21.3. Breaking up sedentary behaviors with short bouts of activity to offset sedentary behaviors adverse health effects

Evidence from population [58, 59] and experimental studies [60, 61] support the scientific premise that reducing total sedentary time and interspersing frequent, short bouts of standing and physical activity between periods of sedentary activity, even in physically active adults seems to lower metabolic risk [60-62]. Independent of total sedentary time and MPVA, taking more frequent breaks in sedentary time was beneficially associated with waist circumference, BMI and 2-h post-meal plasma glucose, highlighting the importance of avoiding prolonged uninterrupted periods of sedentary time [58]. Frequent breaks from sitting may also assist in controlling postprandial spikes prevalent throughout the day in many individuals with T2D, even in those with a glycated hemoglobin (HbA1c) level below 7.0% [63]. Significant improvements in postprandial glycemia and insulinemia have been observed when prolonged sitting interrupted by brief intermittent bouts (microbouts of activity ≤5 min) of light-[60, 61, 64, 65] or moderate-intensity [60] ambulation, with MVPA associated with the most potent health-enhancing time-dependent behavior [66, 67]. These acute experimental studies showed that regular brief interruptions to prolonged sitting can improve cardiometabolic risk markers in healthy, overweight/obese and T2D adults [68].

However, the evidence for the effects on glycemic control of reducing and interrupting prolonged sitting time have largely been acute in nature (mostly <5-7h) (at the time we started our experiments in 2014) and conducted in controlled laboratory settings or derived from population-level evidence. Critical gap in knowledge included **(1)** whether the benefits on metabolic health are due to the breaks *per se* or to the increase in physical activity or TEE and/or the decrease in sedentary time, **(2)** whether the acute metabolic benefits of interrupting prolonged sitting are sustained or diluted over consecutive weeks/months, **(3)** the characterization of the underlying physiological, cellular and molecular mechanisms, **(4)** whether the breaks are a strategy that can be implemented in the daily life of individual at risk or with metabolic diseases. These are the questions I have been investigating for the past 6 years.

21.3.1. What are the short-term metabolic effects of breaking up sedentary behaviors?

In a recent crossover study, Nathan DeJong (PhD student) and I showed in sedentary adults with overweight/obesity that 4 days of frequent interruptions in prolonged sitting with 5-min moderate intensity walking breaks performed every hour for nine hours (MICRO) lead to greater reliance upon carbohydrate as fuel both after a meal and over 24h as compared to a sedentary control condition (Figure 7 bottom) [69]. In contrast, a single isoenergetic continuous bout of 45-min moderate-intensity walking (ONE) increased 24h fat oxidation. Importantly, the two modalities of physical activity induced the same increase in TEE and energy deficit (Figure 7 top) and decreased postprandial insulinemia and fasting HOMA-IR. These findings indicate that when TEE is equal between the two active conditions, breaking up sedentary time impacts daily patterns in fuel utilization differently than when exercise is performed as a single bout, with potentially a more positive effect on carbohydrate metabolism than traditional exercise. Whether these acute effects are maintained over the longer-term was however unknown. Prior to start any longitudinal intervention study, we needed to ensure breaks were a strategy that could be implemented in daily life.

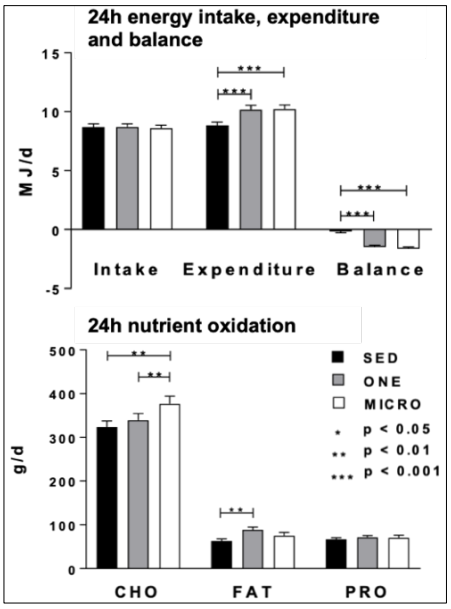

Figure 7 : 24h energy intake, expenditure, balance and nutrient oxidation in sedentary condition (sed), sedentary + 45-min treadmill brisk walking (one) and sedentary + nine 5-min bouts of treadmill brisk walking (micro) in 20 physically inactive overweight/obese adults (10f/10m). CHO, carbohydrates; FAT, fat; PRO, proteins

21.3.2. Can we implement the breaks in people's daily life?

First, we studied the perceived levels of energy, mood, vigor and fatigue in a cross-over study in healthy normal-weight male and female adults who completed three conditions in a random order. They were either sedentary for 6 hours, or completed 30-min moderate intensity treadmill walking as a single continuous bout (ONE) or as six 5-min bouts (MICRO) in a lab setting. Participants reported greater levels of energy and less fatigue at the end of the day after having completed the MICRO condition compared to both ONE and the sedentary control condition [70]. In addition, no effect was reported on cognitive functions suggesting microbouts of activity could be implemented in the work environment, especially in office workers who are vulnerable to the effects of sedentary behaviors. We then confirmed these results in a recent feasibility cross-over study in sedentary overweight/obese people who completed these three conditions for

3 days in free-living conditions on both workdays and non-working days [71]. Altogether these results suggested that microbouts of activity could be implemented in daily life and be enjoyable for both normal-weight and overweight adults.

We recently embarked on a 4-week study during which inactive overweight/obese male and female adults were instructed to perform 45-min of brisk walking as a single continuous bout, 5 days/week, or as nine 5-min bouts spread throughout the day, 5 days/week. So far, all the enrolled subjects (MICRO n=8F/5M; ONE n=8F/6M) have completed the study. The last male subject will complete the MICRO condition at the end of September 2019. To verify compliance, we are providing each subject with a FitBit activity monitor and a personal online account that both the participants and the study team can access. An example of the Fitbit data is illustrated in

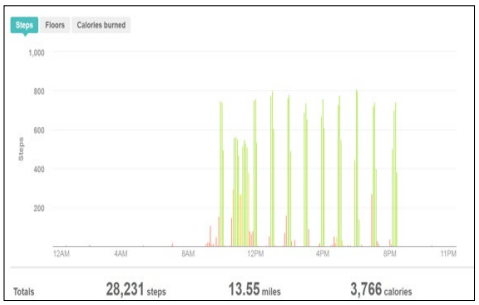

Figure 8. The time during the day and the duration of the bouts match objective data recorded with accelerometers. By checking their online account every day, we are able to give subjects feedback in pseudo real-time, and thus help them reaching the targeted physical activity regimen. So far compliance, calculated as the percentage of days during which the number of instructed bouts is completed, has been of 85±12% and 83±15% in the MICRO and ONE groups, respectively. This data demonstrates our ability to implement these interventions over several weeks in the daily life of participants.

Figure 8 : Example of the FitBit data obtained during a day with microbouts of activity

21.3.3. Are the metabolic health benefits observed after an acute or short-term exposure to the breaks being sustained over time?

In this ongoing study, we are measuring insulin sensitivity at baseline and after 4 weeks of either MICRO or ONE using intravenous glucose tolerance test (IVGTT), daily glycemic mean and variability using a continuous glucose monitoring system (CGMS, Abbott, Freestyle) over 14 days, and 24h nutrient metabolism by combining the use of a whole-room calorimeter and exogenous tracer (U-^{13}C glucose and D_{31} palmitic acid). Preliminary data (MICRO =9, ONE=10) are suggesting that compared to ONE (Figure 9), MICRO improves the acute insulin response to glucose (AIRg) and insulin sensitivity (SI). MICRO further maintains exogenous carbohydrate oxidation at baseline levels while ONE decreases it after 4 weeks (Figure 9). An index of metabolic flexibility is calculated from the chamber data, defined as the difference between the day non-protein respiratory quotient (npRQ, postprandial state) and sleep npRQ (fasting state). Longitudinal changes in this index indicate that MICRO, but not ONE, improves metabolic flexibility (Figure 9). Interestingly, improvements in metabolic flexibility are positively associated with increase in SI (r=0.59, p=0.02). An interaction effect was also observed for postprandial glycemia and insulinemia as well as 24h glycemic variability, suggesting that 4-weeks of MICRO improves these outcomes to a greater extent than 4-weeks of ONE. Finally, MICRO decreased fasting concentration of low-density lipoproteins (LDL) (Figure 9), an atherogenic risk factor often negatively associated with insulin sensitivity [72], to a greater extent than ONE. This preliminary data indicates that breaking up sedentary behaviors improves metabolic flexibility, insulin sensitivity, and glucose control to a greater extent than ONE (unpublished data).

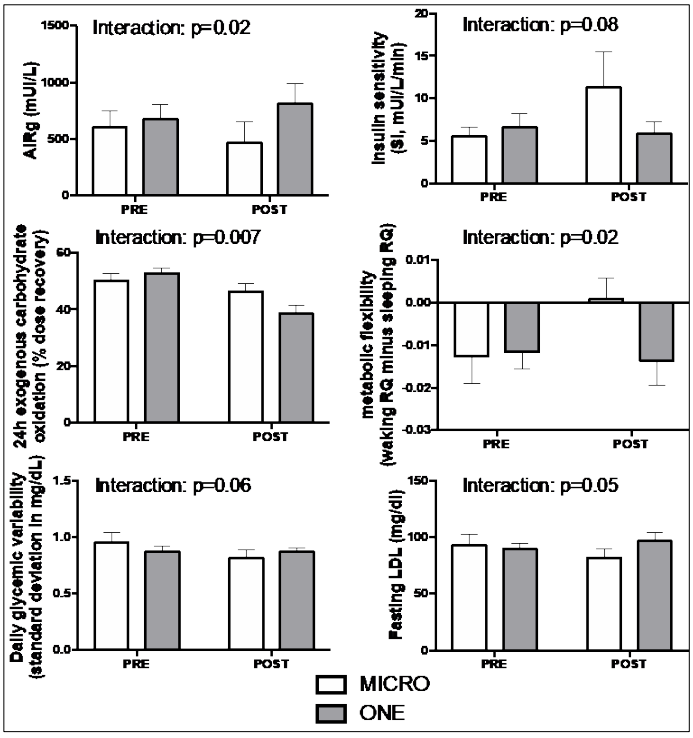

Figure 9 : Effect of 4 wks of microbouts of activity (MICRO, n=9) vs single continuous bouts of activity (ONE, n=10) matched for total active time (45-min) on acute response of insulin to glucose (AIRg), insulin sensivity (SI), 24h exogenous carbohydrate oxidation, metabolic flexibility and daily glycemic variability (standard deviation) in overweight/obese adults. The interaction effect is the interaction between time (pre vs. post) and group (MICRO vs. ONE)

21.3.4. Are the metabolic health benefits of the breaks independent of TEE and time spent active and sedentary?

What is important to keep in mind is that these results have been observed while the last bout of activity had been performed more than 16h before the start of the measurements and while the participants were resting. They are also independent of between group differences between TEE, time spent active and sedentary. By using an accelerometer worn on the hip (ActivPAL) and another one worn on the waist (Actigraph wGT3XBT) over 14 days in baseline and during the last 2 weeks of the intervention, we showed that MICRO and ONE decreased sitting time (-43.5±93.4 min), increased stepping time (+26.3±44.0 min) and time spent in MVPA (+9.8±17.6 min) (**Figure 10**), with no difference between the two interventions. Although not significantly increased, double labelled water (DLW)-derived TEE was also equal between the two interventions (**Figure 10**). Similarly fat mass and fat-free mass remained unchanged and were not different between the two groups (unpublished data).

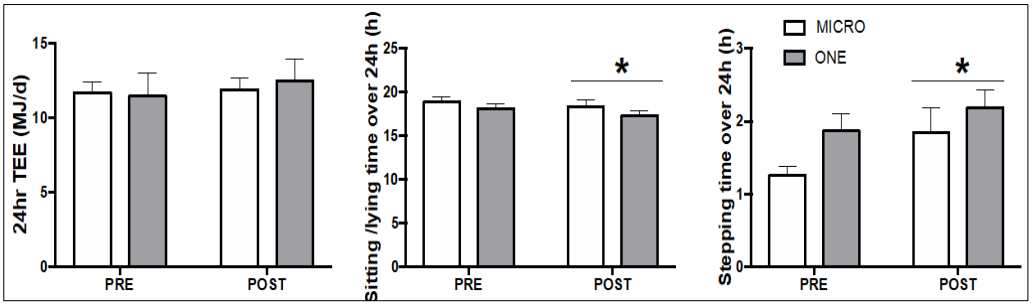

Figure 10: Doubly-labelled water-derived total energy expenditure (TEE), 24h sitting/lying time and 24h stepping time before (PRE) and during the last two weeks of a 4-week intervention (POST) consisting of either nine 5-min brisk walking bouts per day, 5 d/wk (n=9) or of 45-min brisk walking performed once per day, 5 d/wk (n=10). *p<0.05 POST vs. PRE. Not represented on the figure: Stepping time is significantly greater in ONE compared to MICRO in PRE (p<0.05).

To my knowledge, these are some of the first studies that have investigated the longitudinal health effects of breaking up sedentary behaviors on metabolic health over several days and weeks and have demonstrated benefits independent from increase in TEE and or physical activity, and/or decrease in sedentary time and fat mass. The underlying mechanisms remain however unclear and understudied. We have begun to investigate some of them during the short and long-term studies.

21.3.5. What are the mechanisms underlying the beneficial effects of the breaks on metabolic health?

The mechanistic underpinnings of the beneficial effects of breaking up prolonged sitting are likely to be multifactorial and involve peripheral organs that are known to play a key role in the regulation of intermediary metabolism, such as skeletal muscle and adipose tissue.

In response to the acute exposure (5-7h): Before starting my NIH/NIDDK K99/R00 grant fellowship I spent 9 months at the Baker IDI Heart & Diabetes Institute in the Physical Activity Epidemiology & Behavior Lab directed by Neville Owen and David Dunstan thanks to an Australian Government post-graduate research fellowship (2013-2014). During that visit, I have started to study potential mechanisms at the skeletal muscle level that could explain the reduced glycemia observed with the breaks. Skeletal muscle is the largest glucose consuming organ in the body and accounts for more than 80% of the insulin-stimulated glucose disposal and quantitatively the most dominant tissue during exercise [73]. In overweight/obese adults (n=8), we observed favorable changes in skeletal muscle protein expression that likely contribute to the improved glucose control and insulin signaling cascade observed with acute exposure (5h) to breaking up of prolonged sitting via short bouts of activities [74]. This was also associated with greater capacity for glucose storage into glycogen and for ATP production.

Thanks to an NIH BEST International Visitor Scientist Award I went back to the Baker IDI for 3 months end of 2015, before starting my position at the CNRS in France. During this second visit, I collaborated with a post-doctorate fellow, Dr Megan Grace. We observed in the same 8 subjects changes in adipose tissue gene expression associated with improvement in insulin sensitivity and carbohydrate metabolism [75]. These changes include some which align with, and others which are distinct from, the effects of continuous acute exercise [76, 77]. However, these studies were performed in a small sample size not balanced for sex (n=8, 80% male) and after acute exposure (5h) of breaking up prolonged sitting.

In response to the short-term exposure (4 days): We tried to further understand the underlying mechanisms in our 4-days cross-over study. Surprisingly, while no sex differences in physiological adaptations to exercise training have been determined [78], preliminary data in overweight/obese male (n=10) and female (n=10) suggest minor, but detectable, sex differences at the whole-body, cell and gene level in response to 4-days exposure to breaking up sedentary behaviors (unpublished data). While males displayed a reduction in postprandial glucose, as repeatedly reported, an increase was unexpectedly observed in women. By contrast, postprandial triglycerides concentrations were decreased in females but not in males following the performance of 45-min treadmill brisk walking. Using high resolution respirometry in permeabilized fibers from muscle biopsies collected on the morning of day 5 of the study, we further observed that MICRO favors coupling in presence of carbohydrate but uncoupling in presence of fat in males, but not in females. Finally, RNA sequencing performed on muscle from a subgroup of subjects (3M/3F) indicates significant sex differences. Pathways analysis showed that pathways involved in the regulation of insulin signaling (PI3K/AKT and Insulin Receptor Signaling) and nutrient metabolism (oxidative phosphorylation) were activated in males but suppressed in females (**Figure 11**). Altogether these preliminary data obtained at different levels of integration suggest that breaks of sitting are more beneficial for glucose control in men than in women. Future investigations on sex differences in response to breaking up sedentary behaviors are needed to confirm these first results. RNA sequencing analysis are being completed on the other subjects we obtained muscle biopsies on in the three conditions (SED, MICRO, ONE). Based on the results, additional measurement of the protein or gene expression of key proteins will be considered. If confirmed, these results will be important consideration when defining future prescription of physical activity for prevention/treatment of T2D.

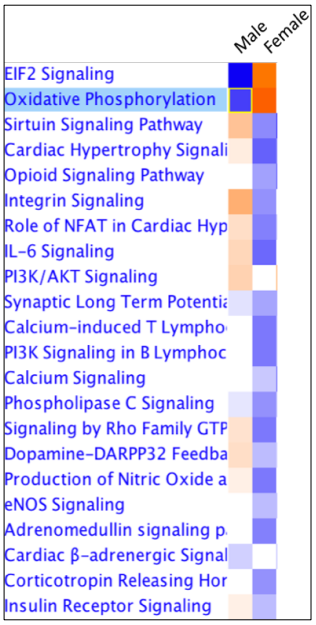

Figure 11. Effect of 4-d breaking up prolonged sitting on the regulation of biological pathways at the muscle level in 3 females and 3 males with overweight. Pathways in blue are up-regulated; those in red are down-regulated.

Project 1: Mechanisms other than those we started to investigate at the skeletal muscle may exist, especially at the level of other organs involved in the energy homeostasis and glucose control (liver, adipose tissue and pancreas). This also implies an inter-organ interaction. I am proposing to investigate these questions in a pilot study in collaboration with Dr Kristen Boyle who belongs to the Department of Pediatrics at the University of Colorado and is an expert in cell metabolism, and Dr Daniel Lark who is an Assistant Professor at the Colorado State University and is an expert in exosomes and inter-organs communication. Details of this multi-PIs research project that will be submitted October 1st are below.

PROJECT 1: WHY SPREADING SHORT BOUTS OF ACTIVITY THROUGHOUT THE DAY HAS MORE BENEFICIAL EFFECTS ON GLUCOSE HOMEOSTASIS THAN PERFORMING A CONTINUOUS BOUT OF ACTIVITY?
A pilot study to identify the potential exerkines associated with these differential effects

SUMMARY/INTRODUCTION: Exercise-mediated multisystemic adaptations are known to mitigate metabolism-related disorders such as T2D. Exercise-induced release of endocrine factors, peptides and nucleic acids from skeletal muscle (myokines) and other organs (collectively termed 'exerkines') has been implicated in mediating these systemic adaptations. A number of myokines has been shown to modulate adipose tissue metabolism, liver endogenous glucose production and β-cell insulin secretion. This cross-talk between skeletal muscle and other organs seems to be dependent on muscle contractions. Recent data from our group suggest that beyond the total daily number of muscle contractions (and/or energy expenditure), how muscle contractions are spread throughout the day influences insulin sensitivity and glucose homeostasis. Indeed, **preliminary data** indicate that whole-body insulin sensitivity, the acute response of insulin to glucose, daily glycemic variability and 24h carbohydrate oxidation, are improved after 4 wks of microbouts (<5 minutes) of activity spread throughout the day (45-min total). The improvements are more pronounced than what was seen with 4 wks of single bouts of activity matched for total active time and energy expenditure. These data support a model wherein microbouts of activity have greater benefits on carbohydrate metabolism than traditionally recommended long bouts of activity. **The potential underlying mechanisms however remain to be characterized.** We **hypothesize** that spreading microbouts of activity throughout the day lead to higher increase in myokines and exerkines, which is associated with greater effects on glucose metabolism at the peripheral organs level, than the performance of a single continuous bout of activity matched for total active time and energy expenditure. In this **pilot study**, we propose to **measure myokines** in plasma from overweight sedentary adults (n=10F/10M) who completed a randomized cross-over study. The three conditions consisted of 3 days in free living conditions followed by 24h in an inpatient controlled setting, and included: (i) sedentary condition (**SED**), (ii) the performance of one 45-min moderate-intensity walking per day (**ONE**), and (iii) the performance of 9 bouts of 5-min moderate-intensity walking per day (**MICRO**). Plasma collected before and after the last bout of activity in the 3 conditions will be used to **incubate human myocytes, adipocytes, hepatocytes and pancreatic beta cell lines**, and respective **metabolic responses** will be measured.

RELEVANCE: This new data will significantly advance the science of T2D prevention and therapeutics, elucidating how spreading short bouts of activity throughout the day improve insulin sensitivity and glucose homeostasis. Building upon this pilot study, future research projects combining clinical intervention studies and *in vitro* experiments will aim at identifying the exerkines that are modifying peripheral organs glucose metabolism.

SPECIFIC AIMS: The overall study design is described in **Figure 12**. Specific aims are as follows:

AIM 1: To determine the myokines excreted in response to ONE and MICRO, compared to SED. Myokines known to modulate the metabolism of peripheral organs involved in whole-body insulin sensitivity and glucose homeostasis such as IL6, FGF21, and irisin will be measured in plasma collected before and after ONE and MICRO. Using an exploratory approach, exerkines will also be analyzed by using an ExoQuick exosome identification system. *H: MICRO and ONE will increase myokines and exerkines compared to SED, but the increase will be more pronounced with MICRO than ONE.*

AIM 2: To determine *in vitro* the metabolic changes induced by the plasma exerkines in the key peripheral organs involved in carbohydrate homeostasis. Human myocyte, adipocyte, hepatocyte and beta cells will be incubated with plasma collected before and after the last bout of activity in SED (no activity, control), ONE and MICRO. *H: Incubation with plasma from MICRO and ONE will lead to greater myocyte and adipocyte glucose uptake, myocyte and hepatocyte glycogen synthesis, hepatocyte glucose output inhibition and pancreatic insulin secretion, compared to SED. Effects will be more pronounced with MICRO compared to ONE.*

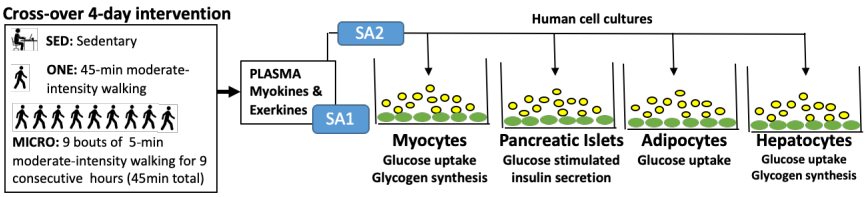

Figure 12. Overall study design

In response to long-term exposure (4 weeks): During the 4-week randomized intervention study, skeletal muscle biopsies are collected on the morning following the 24h stay in the whole-room calorimetry by Dr Bessesen in pre and post interventions. Like for the short-term studies, mitochondrial respiration in presence of carbohydrate or fat substrates is measured by high resolution respirometry (Oroboros). When the study will be completed and based on the final results observed at the whole-body and mitochondrial levels, molecular mechanisms will be studied. We anticipate studying the expression of gene and proteins involved in the regulation of carbohydrate and lipid metabolism but also in insulin and inflammatory pathways. These studies will be part of Nathan Dejong's PhD Thesis and have been proposed in August in an NIH F31 pre-doctoral grant fellowship (PI: N De Jong, Mentors: A. Bergouignan, P MacLean, B Bergman, J Reusch, Z Pan).

Finally, studies show that primary human myotubes, cultured *ex vivo*, retain the metabolic characteristics of their donor [79, 80]. Some groups have shown that exercise training can alter myocyte metabolism in a manner consistent with *in vivo* changes [80-82]. *In vitro* studies can provide mechanistic insight into the skeletal muscle responses to exercise. Also, retained *in vitro* in HSkMC are aerobic exercise training-induced changes in glucose metabolism [81]. Based on this knowledge, we have started to culture primary myoblasts from skeletal muscle biopsies collected in pre and post interventions. This has been conducted in the context of an NIH CCTSI TL1 pre-doctoral fellowship research project (PI: N DeJong) in collaboration with Dr Kristen Boyle (co-mentor). Our goal is to test whether or not the whole-body metabolic changes, especially metabolic flexibility changes, are explained by changes in *ex vivo* metabolic flexibility at skeletal muscle level.

Project 2: Given the published and unpublished results described above, it is important to further delineate the underlying mechanisms that can explain the benefits of breaking up sedentary behaviors on metabolic health independent of TEE, time spent sedentary and active. In this line, I have submitted a 5-year R01 project to the NIH NIDDK in February 2019. Based on the referee's comments, I am going to submit the following project in November 2019.

PROJECT 2: Breaking up sedentary behaviors to improve glycemic control: a mechanistic approach

"Sit Less, Move More" is a new widespread public health message to prevent type 2 diabetes (T2D). Recent epidemiological and experimental studies further suggest that frequently interrupting sedentary behaviors (e.g. sitting) triggers benefits on glycaemic control, which may go beyond those from the increased physical activity *per se*. The underlying mechanisms are however unknown.

Studies by our group and others support the scientific premise that breaking up prolonged bouts of sedentary time may improve glucose control independent of total active and sedentary time. Short-term breaking up sedentary behaviors with short bouts of activity (≤5 min) (i) decreases post-prandial glucose concentrations; even when glucose regulation is impaired, and (ii) stimulates contraction-mediated and insulin-dependent glucose uptake pathways in skeletal muscle. It further increases 24h carbohydrate oxidation whereas a single continuous bout matched for total duration and energy expenditure primarily relies upon fat as fuel. Strikingly, our preliminary data in overweight/obese adults further suggests that post-prandial glycemia and insulinemia, and daily glycemic variability are lowered to a greater extent following 4 weeks of short-frequent active bouts than single continuous bouts of activity despite similar total active time and energy expenditure. Based on these findings and well-established knowledge in exercise physiology, we propose the following working model:

Short, frequent active bouts acutely stimulate both muscle insulin-dependent and -independent pathways along, promoting oxidative and non-oxidative glucose uptake, resulting in greater carbohydrate use. Chronically, this induces the genetic/transcriptomic machinery that stimulates glucose uptake and oxidation, a benefit that is sustained in resting conditions. This improves the ability to use carbohydrate as substrate following a meal, thus lowering post-prandial glycemia and its daily variability, which are key features of T2D. In contrast, single continuous bout of activity stimulates fatty acid metabolic pathways both acutely and over time.

Our objective is to characterize the mechanisms underpinning the beneficial effects of the breaks on glucose control observed in our 4-wk preliminary study. Sixty sedentary male and female adults with overweight/obesity and prediabetes will be randomly assigned to one of two 4-wk interventions: breaking up sedentary time with short bouts of activity (MICRO), or a daily bout of continuous activity (ONE) which is matched for total active time (45 min/d, 5 d/wk). Our central hypothesis is that MICRO will be more beneficial for glycemic control than ONE in adults with pre-diabetes. To test the central hypothesis and accomplish the overall objective of this proposal, we will pursue the following 3 independent specific aims:

Aim 1. To establish the *in vivo* effects of 4 weeks of short-frequent bouts of activity versus single continuous bouts of activity on the ability to efficiently switch from fat oxidation in fasting to carbohydrate oxidation in response to a high-carbohydrate (HC) metabolic challenge.

We hypothesize that MICRO will increase the ability to switch from fat oxidation in fasting to carbohydrate oxidation following HC meals, and thus to lower post-prandial glycemia and daily variability, to a greater extent than ONE. This will be tested by measuring total carbohydrate and fat oxidation by whole-room calorimetry, and plasma glucose concentrations in response to HC meals at baseline and after 4 wks of either MICRO or ONE.

Aim 2. To establish the *in vivo* effects of 4 weeks of short-frequent bouts of activity versus single continuous bouts of activity on systemic and tissue-specific insulin sensitivity and glucose uptake.

We hypothesize that MICRO will improve whole-body and muscle insulin sensitivity to a greater extent than ONE, due to greater muscle glucose uptake. This will be tested by using a 2-stage hyperinsulinemic-euglycemic clamp coupled to a stable isotope glucose tracer infusion at baseline and after 4 wks of either MICRO or ONE.

Aim 3. To establish the *in vitro* effects of 4 weeks of short-frequent bouts of activity versus single continuous bouts of activity on skeletal muscle fuel switching ability.

We hypothesize that MICRO will increase the ability to adjust substrate selection in response to changes in acute glucose and fatty acid exposure in myocytes, to a greater extent than ONE. Primary myoblasts will be cultured from fresh skeletal muscle biopsies collected in fasting state at baseline and after 4 wks of either MICRO or ONE. *In vitro* experiments will determine cellular glucose and fat uptake, oxidation and insulin sensitivity. Regulation of associated metabolic pathways will be determined.

Exploratory Aim: To test the feasibility and efficacy of implementing this novel strategy over 3 months.

The MICRO and ONE interventions will be prolonged for 2 months in the daily life of participants. Adherence and key clinical health outcomes (eg. HAb1c, hyperglycemia, daily glycemic variability) will be compared.

Impact: This study will provide robust rationale for implementing breaks in public health recommendations for T2D management that goes beyond the well-known effects of physical activity.

This work on the health effects of breaking up sedentary behaviors has been my main research project for the past 6 years and has been conducted at the University of Colorado since 2013. Since 2017 it is being conducted in the context of a Joint International Lab ("Laboratoire International Associé or **LIA**") I am leading between the University of Colorado and the CNRS-IPHC (please see 'Research Management Activities' section for further details). It has been the result of numerous funding and productive collaborations. Specifically, the work on the acute effects of breaking up sedentary time on self-perceived energy, mood, vigor/fatigue and cognitive function was funded between 2013 and 2014 by the Johnson & Johnson Company in the US (PI: Daniel Bessesen) and I served as a co-investigator. The work on the short- and long-term metabolic effects of breaking up sedentary behaviors has started in 2014. For this work I received an NIH NIDDK K99/R00 Pathway to Independence Award (2014-2019) that is the equivalent to the European Research Council (**ERC**) Starting Grant. In addition, I received two internal pilot studies grants, one from the Colorado Clinical & Translational Sciences Institute (**CCTSI**) and the other one from the Colorado School of Public Health, two microgrants from the University of Colorado Clinical & Translational Research Center (**CTRC)** and two additional funding from the University of Colorado. These funding represent a total of $1.41M. This research has also been possible thanks to the work of two undergraduate students (C. Mendez and L Schreck), four Master's students (A. Lange, T. Glazer, H. Hamidu and L. Schreck), three PhD students (N. De Jong, I Debache and M Garnotel) and the help of the nurses, dietitians and staffs of the CTRC. It has been conducted in close collaboration with Dr Daniel Bessesen who has served as the study physician for the acute, short-term and long-term studies. I also collaborated with Dr Kristina Legget from the Department of Psychiatry at the University of Colorado for the measurement of cognitive functions, Dr Edward Melanson for the study visits in the whole-room calorimeter, Dr Corey Rynders from the Geriatrics Department for the metabolic flexibility approach, Dr Josiane Broussard for the interpretation of the IVGTT data, Dr Matthew Jackman for the mitochondrial respiration measurement, and Dr Michael Rudolph for the RNA sequencing.

If the regulation of metabolic health likely depends on factors others than or in addition to TEE and time spent physically active, body weight is directly regulated by energy balance which is the difference between energy intake and TEE. To understand how body weight is regulated it is therefore important to understand how each of the components and subcomponents of energy balance are regulated, as well their interactions and respective contribution to body weight control.

22. How does contrasted manipulation of physical activity influence TEE and ultimately energy balance?

The LIPOX data described above (**Figure 6**) supports the existence of spontaneous compensatory behaviors, i.e. decrease in non-activity energy expenditure, in response to exercise training and energy balance [55]. This has been observed in other studies but not all as reviewed by Ed Melanson [83]. It is partly because of this lack of impact on TEE and energy balance that exercise is considered as an inefficient strategy to control body weight. We however think that conclusions may have been drawn too rapidly and further studies, especially through the prism of evolution are needed.

Project 3: This represents an ongoing research project () that has begun with the funding from the "Mission Interdisciplinaire" CNRS pilot award, and that is now becoming the topic of a PhD Thesis starting October 1st, 2019 (P Bourdier) thanks to a 3-year graduate school pre-doctoral fellowship he secured under my mentorship.

Project 3: testing evolutionary medicine concepts: is total energy expenditure homeostatically regulated in humans?

BACKGROUND: Evolutionary medicine, increasingly used in public health, provides new insights into the etiology of obesity, diabetes, and other chronic diseases. The evolutionary approach assumes that over the millennia, natural selection has shaped the human body under specific environmental and ecological conditions. The rapid and recent changes in our environment induced by the industrial and technological revolution have created an imbalance between the environment and our biology, which has led to the emergence of chronic diseases. The regulation of the energy balance, i.e. the difference between intake and TEE, has remained surprisingly poorly studied by scientists in the evolutionary biology field of research. This is especially true for TEE. Additive models of TEE (factorial models) currently dominate the field and consider TEE as a simple product of body size and physical activity without taking into account the potential regulations between the different components of TEE. Recent data suggest, however, that TEE is a relatively stable parameter, homeostatically controlled, that better reflects our evolutionary past than our modern way of life. This new constrained TEE model suggests that a high increase in physical activity triggers compensatory mechanisms to maintain stable DET. This questions the current knowledge on the regulation of energy balance in humans and could explain, in part, why the exercise has only a very limited effect on weight loss. Understanding the regulation of TEE would provide key data for a better prevention and treatment of obesity and related diseases. To test this question, it is important to accurately measure TEE and its components, as well as daily physical activities in terms of cost, type, duration, intensity, and frequency.

APPROACH: We propose to test this hypothesis by combining data from studies during which participants are engaged in very high or very low levels of physical activity for several days or several weeks. TEE and its components will be measured by combining the use of the doubly labeled water method with indirect calorimetry. Body composition will be measured by impedancemetry. The physical activity profile will be measured with accelerometers coupled to recently developed algorithms. Energy intake will also be tightly controlled. Studies we propose to use are studies that have been completed (Arctic expedition – see details below, or long-term spaceflights and bed rest studies) or that will need to be conducted (e.g. Marathon des sables or others).

22.1. Regulation of TEE in response to very high levels of physical activity during an Arctic expedition?

As proposed in **Project 3**, studying TEE and its components in extreme conditions where physical activity is very high or very low can bring valuable information to understand the regulation of TEE. The Arctic expedition proposed in this project has been completed, and data and samples analysis is still ongoing. The initial goal of this project was to understand the energy needs and adaptations of women's energy metabolism who participated in a polar expedition during which they were facing very low ambient temperatures, constant daylight, and were engaging in intense physical activity while pulling a sled weighing over 50 kg. This was the first physiological study in women during a polar expedition.

The study took place in April 2018 as part of The Women's Euro-Arabian North Pole Expedition 2018 (http://www.euroarabianexpedition.com/). This expedition was led by Felicity Ashton, who is the first person in the world to have crossed Antarctica autonomously and who spent the most time in the polar regions. These exploits placed her in the Guinness Book of Records. She initiated this expedition to bridge the gap between Europe and the Middle East regions and inspire women to achieve their dreams and be more than what society expects of them. It brought together 11 women from Russia, France, England, Slovenia, Cyprus, Saudi Arabia, Kuwait, Sweden, Qatar, and Oman (**Figure 13**). These women were not athletes and had no experience with the polar regions before this expedition.

Data collection before and after the expedition took place at Longyearbyen Hospital in Svalbard (Territory under the direction of Norway) as well as during the expedition by the participants themselves. Energy metabolism was measured by DLW and indirect calorimetry (**Figure 13**), body composition by bio-impedance spectroscopy (**BIS**), physical activity by 3D-accelerometry, surface body temperature by i-Buttons, circadian cycle by sequential saliva sample collection, and plasma parameters by blood sampling.

Preliminary results indicate that a polar expedition induces very high levels of energy expenditure (**Figure 13**), which are equivalent to the TEE measured in runners of the Tour de France, one of the most demanding sporting events on Earth. However, this high energy expenditure is not due to very vigorous activity, but to the fact of moving slowly all day long (unpublished data).

Beyond the information it will provide to address the question of the regulation of TEE, this study also brings new data in the field of extreme physiology. While 15% of our planet is habitable, 85% is composed of water, desert, ice or mountains. Studying how humans manage to visit or live in these hostile environments such as space or frozen poles helps us to understand how the body adapts to extreme environmental conditions. Such studies also provide unique information that can improve our understanding of certain diseases, such as aging or sports performance.

For this study I composed a team of female scientists and physicians from the Arctic University of Norway (S. Bourgeon), the CRNH Lyon (C. Simon), the University of Colorado (J Devitt) and the Veterinary School of Maison Alfort in France (C. Gilbert). The goal was to match the all-female expedition. We were proud to complete this study despite numerous unexpected events that threatened multiple times the success of the study, as described in the WIRED magazine by a journalist who followed us the whole time (https://www.wired.com/story/inside-all-female-trek-to-north-pole/).

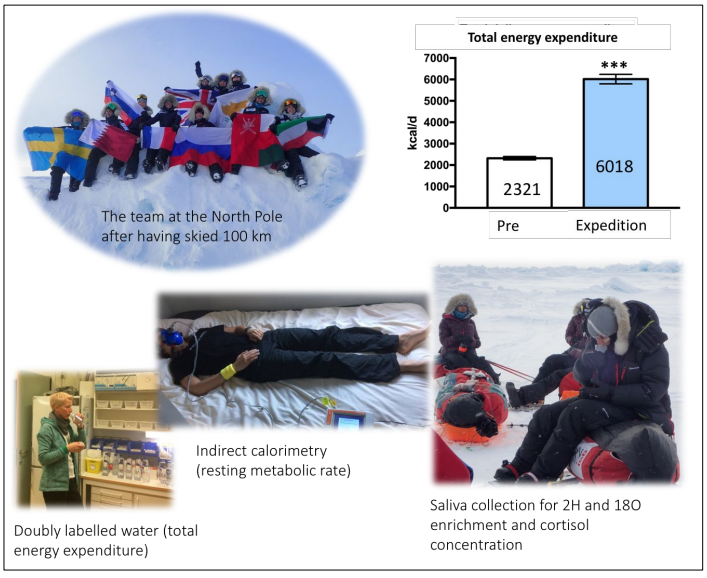

Figure 13. Measure of total energy expenditure and its components before and during a 10-day artic expedition in female adults

22.2. Regulation of TEE and subcomponents in response to very low levels of physical activity along with an intense exercise training protocol during a long-term spaceflight?

The ENERGY study (PI: Stéphane BLANC) aimed to estimate the energy needs of astronauts during long-term space flights. Between 2010 and 2018, we studied before and after 3 months in-flight TEE and its components (resting metabolic rate or **RMR**, diet-induced thermogenesis or **DIT** and AEE) in 10 astronauts by combining the use of DLW method and indirect calorimetry. We observed two groups: those whose TEE had increased (n = 5) and those whose TEE had decreased (n = 5) after three months in the ISS compared to pre-flight values (**Figure 14**). Variations in TEE are not explained by changes in RMR or DIT, but by variations in AEE. Astronauts whose TEE increased maintained their lean body mass as expected, but lost fat mass. On the other hand, astronauts whose TEE has decreased have not lost fat mass but have not maintained their fat-free mass either. Changes in body fat and fat-free mass were closely related to changes in AEE. However, only the time spent in aerobic exercise, and not in resistive exercise, was related to fat loss (unpublished data). This work was led by S. Blanc and was funded by the CNES. I served as a co-investigator.

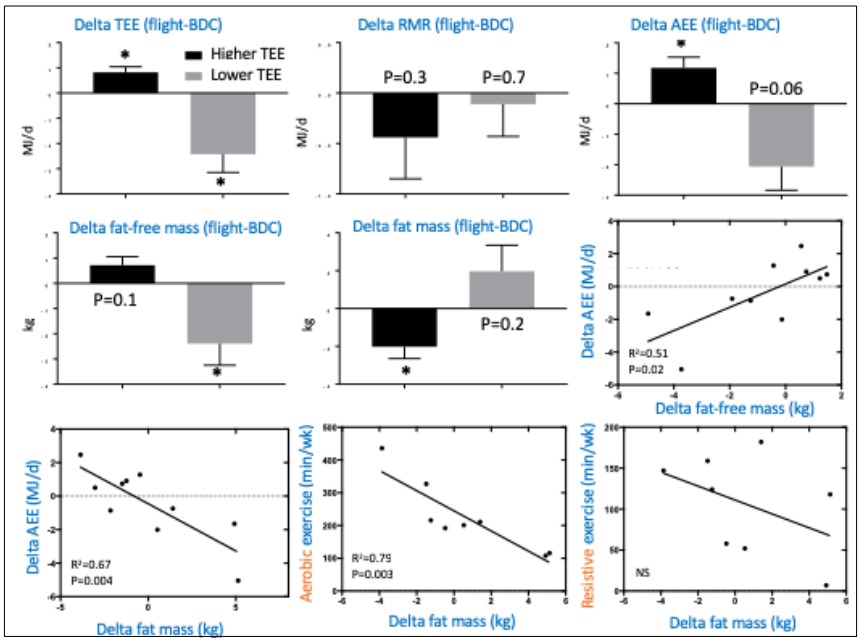

Figure 14. Exercise and energy balance during spaceflights. Changes in total energy expenditure (TEE), resting metabolic rate (RMR), activity energy expenditure (AEE), fat-free mass and fat mass after 3-months on the ISS from before the flight (BDC) values. Correlations between delta AEE and delta fat-free mass and fat mass, and between time spent performing aerobic and resistive exercise and fat mass.

These data are particularly interesting because they suggest that exercise disrupts energy balance regulation in space and that the increase in energy expenditure induced by physical exercise is not accompanied by compensatory changes in energy intake to match energy requirements, resulting in negative energy balance (at least for some of them). This suggests that in space 24h TEE is the main driver of body mass changes, because energy intake cannot match it. This is contrary to what is observed on the Earth where body weight loss is essentially reached by decreasing food intake (without spontaneous concomitant reduction in 24h TEE) rather than by increasing TEE [84-86]. On Earth, non-exercise AEE even decreases in response to an exercise training program, as we showed it in overweight/obese individuals (**Figure 6**) [55], which seems to counteract the effects of exercise on TEE. Altogether these observations question the role of exercise in the regulation of energy balance in space and suggest that energy expenditure plays a key role in body mass control. One of the post-doctorate fellows I co-mentor (C Laurens) has recently compiled all these data in a review to summarize how energy balance and its components are regulated in space [87]. In this review, we further challenged the dogma of must-do exercise countermeasure, at least in its current form, as it is automatically prescribed by the International Space Agencies to prevent the body from the adverse health effects induced by the space environment.

Project 4: In this context, I have recently submitted a research project to the European Space Agency (**ESA**) that is currently being reviewed.

Project 4: Optimizing the exercise countermeasure to prevent the microgravity-induced adverse health outcomes without inducing energy deficit: a pre-requesite study for planetary exploration

Energy requirements during space flight are assumed to be similar to those on the ground [88, 89] provided that exercise countermeasures are well accounted for. Yet astronauts consume less food than needed to cover their TEE [88, 90, 91], which induces body mass loss. A meta-analysis of the LSDA based on 619 missions estimated an average loss of 2.4% BM per 100 days spent in space [92]. A mission to Mars could induce >15% loss of initial BM. This loss is of medical concern given that energy deficit can exacerbate some of the deleterious physiological changes observed during space flight including cardiovascular deconditioning, bone density, muscle mass and strength losses, impaired exercise capacity, and immune deficiency [93]. This may jeopardize crew health and performance, a healthy return to Earth and mission's success. Achieving energy balance during long term space flights becomes a research and operational priority.

Specific Aims & Hypothesis: The **overall objective** of this proposal is to challenge the current prescription of exercise countermeasure (**CM**) and test an alternative protocol that would effectively mitigate adverse health effects of microgravity while maintaining energy balance. Using a randomized intervention study design, we propose to compare the effect on bone and muscle mass, muscle strength, metabolic health and energy balance of two protocols of exercise CM: (1) traditional training that will consist of 2-3h/d of combined aerobic and resistive exercise, as currently prescribed, and that is known to increase TEE (n=6), and (2) an innovative training that will consist of a HIIT protocol that will induce an energy expenditure 35% lower than the one induced by the aerobic exercise, in combination of resistive exercise, for a total duration of 1-1.5h/d. Compliance will be verified using the astronaut's activity log and ideally if possible using a wrist connected device during the spaceflight. The **central hypothesis** of this project is that the innovative exercise CM will maintain bone and muscle mass, muscle strength and biomarkers of metabolic health at their pre-flight levels without inducing a negative energy balance, as indicated by fat mass loss, contrary to the traditional exercise CM during a short-term space flight. Furthermore, it will be less time consuming and associated with better self-perceived mood and vigor and less fatigue. The **specific aims** (SA) and **hypothesis** (H) are as follows:

SA1. To compare the effect of traditional vs innovative exercise CM on body and fat mass.
H1. The innovative CM will lead to lower body and fat mass loss, measured with a calibrated scale and DXA respectively in pre and post flight, as compared to the traditional exercise CM.

SA2. To compare the effect of traditional vs innovative exercise CM on bone mass, muscle mass and muscle strength.
H2. The innovative and traditional CMs will maintain to a same extent bone and muscle mass and muscle strength, respectively measured by DXA, non-invasive D3-creatine dilution method and arm grip strength and leg press in pre and post flight.

SA3. To compare the effect of traditional vs innovative exercise CM on biomarkers of metabolic health and overall well-being.
H3. The traditional and innovative CM will prevent to a same extent the microgravity-induced adverse effects on metabolic health, as indicated by non-significant changes in biomarkers of metabolic health (fasting glucose, insulin, triglycerides, HDL, LDL, IL6, C-reactive protein, transaminases) during short-term space flights. However, astronauts in the innovative CM group will report less deterioration in mood, vigor and less fatigue than those subjected to the traditional CM.

Innovation & Impact: This research project will provide important and novel information to better plan astronauts' exercise CM protocols and nutrition for future planetary exploration, which will have implications for the health and performance of the astronauts, and the success of the missions.

Research in real microgravity conditions provides unique data. Astronauts represent a population subject to an experimental paradigm that is difficult to create on Earth but mimics the current situation. Indeed, in our contemporary societies, recommendations on physical activity are available on sport and MVPA. While these activities improve health, they do not replace everyday activities that are characteristic of our ancestors' lifestyles. Similarly, astronauts are subjected to very high volumes of exercise while being completely sedentary. This research allows us to better understand the regulation of energy metabolism and weight and to recreate the effects of our current ecological niches on the organism. In this way, they help to better understand how urbanization and environmental changes in recent decades that have promoted sedentary behaviour and physical inactivity contribute to the aetiology of chronic diseases.

23. What is the role of physical activity, diet, lifestyles/culture in the regulation of body weight and metabolic health?

Despite large initiatives developed across the globe to manage obesity, its prevalence reaches epidemic levels. A potential reason is that the complex interactions between the biological, behavioral, and socio-ecological factors as well as their respective role in the regulation of body weight is still not well understood. The epidemiological transition model summarizes the changes in nutrition, physical activity and culture/lifestyle that initiated the onset of obesity in Westernized countries. Studying in real-time populations from pre-industrialized countries where the epidemiological transition is ongoing is an ideal paradigm to determine the causes of the obesity epidemic. The Fulani people living in Senegal offer the exceptional opportunity to address this question. They are composed of sub-populations who are at different stages of the epidemiological transition, i.e. those living in urban environment (Dakar) and those living in rural environment (Ferlo) either in villages with access to diverse food and a borehole for water, in camps at 10-15km of a borehole, or in camps where a borehole will be built in 2020, which will dramatically accelerate the impact of the transition (**Figure 15**). Those in the Ferlo are nomadic people, known to leave for long months in transhumance, and are still in the process of settling down. This population offers a unique opportunity to understand the impact of major changes in lifestyles, diet and physical activity induced by urbanization and epidemiological transition on weight regulation.

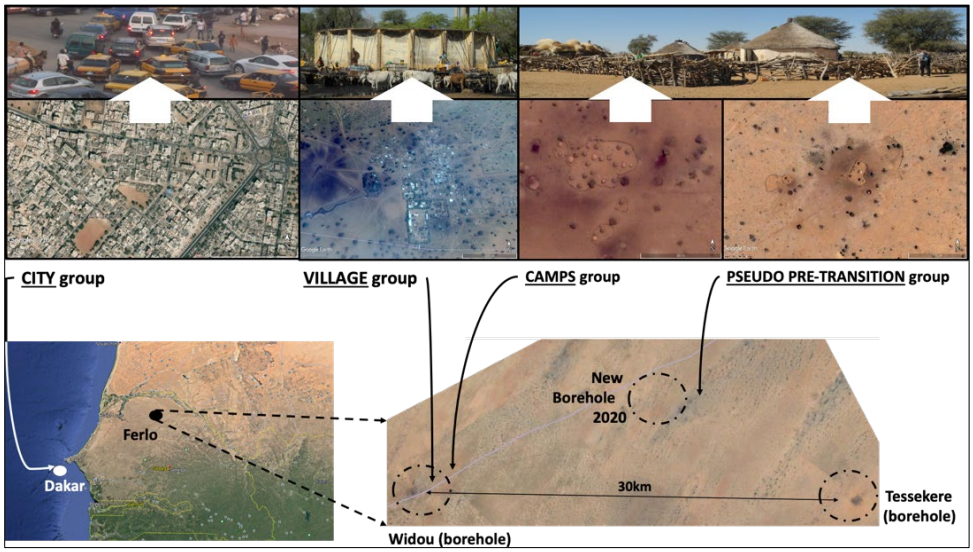

Figure 15. Geographical locations and stages of the epidemiological transitions (urbanization as shown by googlemap pictures) **of the sub-populations of interest, i.e. City group, village group, camps group and pseudo pre-transition group.**

This project began in January 2016 and is conducted in close collaboration with the bio-anthropologists of the UMI 3189 CNRS (E Macia and P Duboz), the Observatoire Homme Milieux (OHM) Téssékéré and the CRNH of Lyon (C Simon). To date, it has been the subject of four field campaigns, two in the Ferlo (Sahel Desert in the Six Wells Region) and two in Dakar. The second campaign in Dakar took place from the 20th to the 31st of August 2019. This research has received funding from Danone (PI: S Blanc) for which I am a co-investigator. We also received a one-year salary for a post-doctorate fellow. We recruited a bio-anthropologist (E. Cohen) who had a great deal of experience with field work in Africa. During this post-doc fellowship, E Cohen has been recruited as a permanent researcher at the CNRS; starting date is October 2019.

First results have been obtained in 49 rural young male Fulanis (37.8±10.6 years; BMI 20.6±3.7 kg/m2) who live in a traditional-pastoral lifestyle and in 27 urban young male Fulanis (37.3±11.3 years; 19.9±3 kg/m2) who have lived in Dakar for at least 10 years. Using 3D-accelerometers and automatic posture recognition algorithms [94], we are showing that Fulanis living in urban environment spend more time sitting and in prolonged sedentary bouts, but are less engaged in walking/running activities than those living in a rural environment. The next steps are to **(1)** characterize the longitudinal changes in physical activity and sedentary behaviors, **(2)** understand the simultaneous changes in diet, lifestyles and cultures, and **(3)** explore the associations of these changes with key parameters of metabolic health and body weight.

Project 5: I have recently received an award from the French Society of Nutrition (**SFN**) to pursue this project. However, major funding is needed to properly conduct this interdisciplinary project. We have applied in 2018 and 2019 to the French National Foundation (**ANR**). Although we were short-listed in 2018, we did not receive funding. We are applying again in 2020. I am a Co-PI on this project along with S. Blanc. This is the **Project 5** detailed below.

Project 5. Revisiting the role of physical activity in weight regulation: an ecological study at the crossroad between cultural anthropology and nutritional physiology in Fulani nomad pastoralists in Senegal

The constant increase in the global prevalence of overweight and obesity indicates that decades of intensive efforts developed across the world to reduce and treat obesity have failed [95]. Possible explanations may reside in the fact that the past socio-ecological transitions that initiated excess weight gain in our modern industrial societies ended decades ago. This has made challenging the contemporary study of the determinants of obesity. **The goal of TRANSITION is to understand the respective contribution of the biological, behavioral and socio-eco-anthropological factors to the global obesity epidemic.** To do so, we will study a pre-industrial population currently facing major socio-ecological transitions, the Sahelian Fulanis semi-nomadic pastoralists living in Senegal.

The diet, demography, health and physical activity transitions are often reunited in the concept of epidemiological transition, i.e. the change in the pattern of mortality and disease from high children mortality and infectious diseases to chronic diseases. How these transitions impact the social, ecological, biological, behavioral and cultural factors associated with diet and physical activity, and ultimately weight regulation, are part of the debate on the etiology of obesity. Rather than being independent we believe the effects of those transitions are progressive and synergistic.

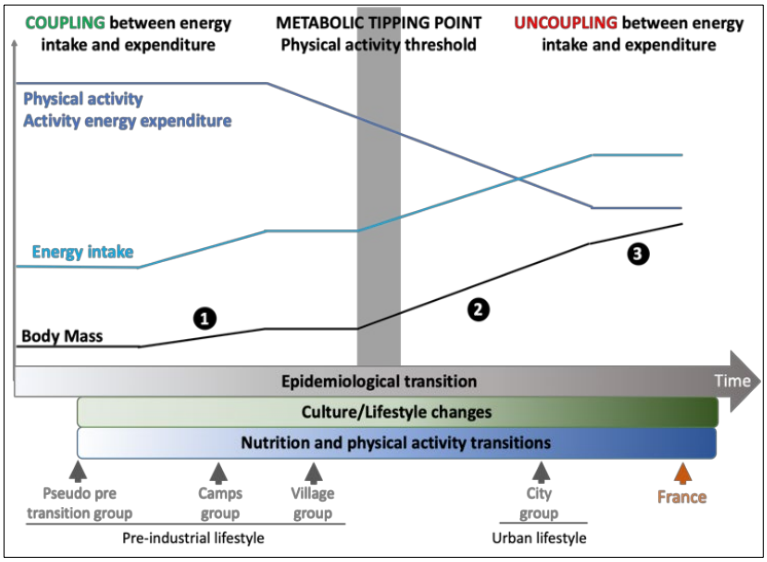

Figure 16. Overall working model. Position of the groups on the transition gradient are arbitrary and indicative.

Our **central hypothesis** and **working model** (**Figure 16**) is that ❶ During the first phase of the nutrition transition, improvement in food intake, i.e. increase in protein, micro-nutrients and energy intake, decreases the prevalence of under-nutrition and malnutrition. Healthier food intake improves the ability of the body to adapt to physiological stresses and increases BW to healthy values. **Energy expenditure and intake are coupled** so that *expenditure drives intake,* and body weight (**BW**) remains *stable*. However, high sugar and fat content and excessive salt start to appear in the diet. ❷ During the physical activity transition, physical activity drops, which decreases AEE beyond a threshold corresponding to a metabolic tipping point. This is associated with an alteration of the regulatory mechanisms of food intake leading to **an uncoupling between energy intake and expenditure**. *Energy intake then drives directly body and fat mass (**FM**), which progressively increase*. ❸ With more advanced technologies as those present in Westernized countries, additional factors such as poor sleep hygiene, endocrine disruptors, increased stress, altered social structures and interactions, come at play and further influence the regulation of BW and FM.

We propose **to test this central hypothesis by using a unique interdisciplinary and systemic approach that will be at the interface of anthropology, sociology and biology/physiology.** However, this can obviously not be done in our westernized societies (e.g. France) as our socio-ecological transitions have ended decades ago. **Instead, we propose to study one of the last populations who have maintained a pre-industrial lifestyle: the semi-nomad pastoralist Fulanis of Senegal.** This population is composed of sub-populations who have maintained a pre-industrial lifestyle in the Ferlo region but who are at different stages of the epidemiological transition (Pseudo-pre transition, Camps and Village groups). Because of upcoming environmental changes, we expect the pseudo pre-transition group, who is at the very early stage of the transition, to undergo an accelerated transition. On the contrary, some Fulanis from the Ferlo have moved to the capital more than 10 years ago and been exposed to an urban lifestyle since then (City group). Importantly all these sub-populations share the same genetic background. **These unique characteristics allow for the opportunity to track in real-time the behavioral, social and biological changes induced by the early stages of the epidemiological transition to dissect the respective role of diet, physical activity and culture on the regulation of adiposity and biomarkers of health.**

We propose to perform a **cross-sectional study** by comparing the groups who have maintained a pre-industrial lifestyle but at different stages (3 *Pre-industrial groups*) to a group who lives in an urban and modern environment (*City group*).

In a **longitudinal study**, we will subsequently follow-up these same four groups over a 3-year period. For each axes of research, **specific hypotheses are as follows**:

Energy expenditure, physical activity pattern and adiposity

1.a) At baseline, **(i)** total energy expenditure (**TEE**) and AEE, as measured by the combined use of doubly labelled water (**DLW**) and indirect calorimetry, will be higher in *Pre-industrial groups* than in the *City group*, with substantial differences in activity patterns, as measured by accelerometry and GPS; and **(ii)** AEE and FM, measured by bio-impedancemetry (**BIS**), will be negatively associated.

1.b) Over 3 years, **(i)** physical activity patterns will change in the *Pre-industrial groups*, especially the *Pseudo-pre-transition* one, leading to a decrease in AEE; and **(ii)** changes in AEE will be negatively associated with changes in FM across the groups.

Energy intake, dietary pattern, and metabolic health

2.a) At baseline, diet of the *Pre-industrial groups* will have lower diversity, and include less energy-dense food, fat and salt than the diet of the *City group*. Diet and feeding patterns will be assessed by food-frequency questionnaires, 24h-recall, continuous glucose monitoring and ^{13}C and ^{15}N isotopic enrichments in hair.

2.b) At baseline, metabolic profiles (waist circumference, visceral fat, blood pressure, glycemic and lipid profiles) will be healthier in the *Pre-industrial groups* than in the *City group*, while protein and micronutrient nutritional status will be less healthy.

2.c) Over 3 years, the diet *of the Pre-industrial groups,* especially the *Pseudo pre-transition* one, will become more diverse, shift from vegan to animal protein diet, and have an increase in energy-density, fat and salt content, and glycemic index.

2.d) Over 3 years, nutritional deficits will be reduced but metabolic health will be deteriorated in the *Pre-industrial groups,* especially the *Pseudo pre-transition* one, in association with changes in AEE, and physical activity and dietary patterns.

Socio-anthropological dimensions and synergistic interactions

3.a) At baseline, social representations and practices of physical activity, diet and body weight will differ along the transition gradient. The *City group* will associate more physical activity practices and low-calorie food with health as a preventive reaction to the obesogenic urban area, although rural representations valuing food abundance and stoutness may persist in less educated urban people. The *Pre-industrial groups* experiencing relative food restrictions will value these dimensions as symbols of health and devalue specific physical activities as sport since their daily manual labors already require an important physical effort.

3.b) Over 3 years, changes in conditions of existence in general, in social and professional activities in particular, will affect the social representations and behaviors towards diet, physical activity and BW, in the *Pre-industrial groups,* especially the *Pseudo pre-transition* one. They will adopt representations closer to those observed in the City group.

3.c) The ultimate hypothesis is that, over 3 years, physical activity and diet patterns, energy expenditure and intake, and socio-anthropological factors will interact with each other and contribute synergistically to excessive FM gain and metabolic alterations.

To test these specific hypotheses, we will determine the **cross-sectional** between-groups **differences** and **longitudinal changes** in **(i)** BW, FM and metabolic health outcomes, **(ii)** TEE, energy intake, and metabolism, **(iii)** physical activity and feeding behaviors, and **(iv)** culture and lifestyles induced by the recent and ongoing epidemiological transition in the Ferlo. This will contribute to improve our understanding of the **socio-ecological** and **behavioral determinants** of BW gain, and thus identify future health guidelines to fight against the global obesity epidemic.

CONCLUSION REMARKS

"Sitting is the new smoking", "Sit Less, Move More, More Often", "Your chair is killing you", "Move", "Do your 10,000 steps per day" are messages that keep being thrown at us both by the media and public health campaigns. As a result, we are seeing an incredible number of pedometers being marketed along with applications to use on smart phones to track our daily physical activity and time spent sedentary. Despite these new devices, our modern populations keep being more sedentary, and less active. The phenomenon is becoming global and will likely accelerate with the increasing urbanization phenomenon of the low- and middle-income countries.

This trend will likely have dramatic health, economic, societal and environmental consequences. The challenges to reverse it are multiple. Like with nutrition, many preconceived ideas persist about what sedentary living is and how to deal with it. Because sedentary behaviors are ubiquitous, everybody has an opinion and believes it is already well understood. Research on this topic is therefore not perceived as a priority and sometimes as "a science of low level". The problem is also cultural and political, and both will need to be changed to address this public health burden.

This is what happened in the 1990s-2000s with smoking. Although it was clear that smoking was the cause of cancers, it is only once scientists accumulated a large body of robust data demonstrating the cause-and-effect relationships that public health guidelines and governments introduced new policies making all public spaces as non-smoking areas for example. Nowadays, it has become inconceivable to smoke in a restaurant for example. A similar scenario may happen with sedentary behaviors in the 2020s. The task may be even more challenging given the accelerated race to innovation that keeps placing convenience as a priority, which results in engineering physical activity out of daily life.

Our inability to slow down the metabolic disease pandemics demonstrates the high level of complexity of the physiopathology of sedentary behaviors and physical inactivity and of the regulation of body weight and metabolic health. This is why scientist need to provide solid, irrefutable and rigorous evidence proving the adverse health effects of sedentary behaviors and physical inactivity, and the underlying mechanisms. These investigations also need to be conducted in multidisciplinary and interdisciplinary studies that will investigate the different factors influencing body weight and metabolic health, such as individual predisposition, environmental, socio-ecological and anthropological factors. It is only by adopting a thorough and rigorous socio-ecological approach, we will be able to convince police makers to take clear actions to prevent sedentary behaviors and the associated diseases.

It is in this direction I want to pursue my research program for the next years. The research projects I have proposed or plan to propose soon will build upon my past research findings and bring the next body of data to help preventing sedentary behaviors and associated metabolic diseases (**Figure 17**). By doing so, I hope to contribute to improving human condition.

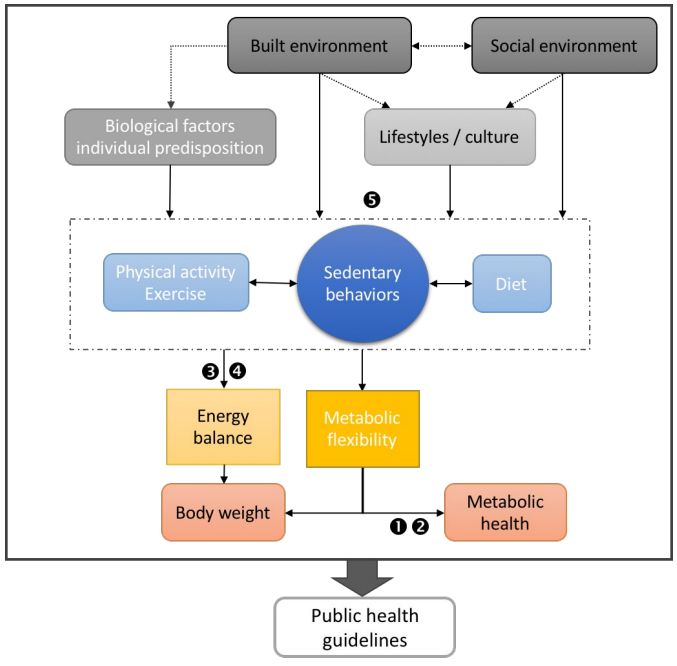

Figure 17 : Summary of my research program project and the questions addressed by the five research projects I am currently working on or proposing to work on.

RESEARCH MANAGEMENT ACTIVITIES

Following the start of my K99/R00 award in September 2014, I have developed my own lab at the University of Colorado. I received 50m^2 of shared wet laboratory space with all the major resources needed in a lab. I hired a personal research assistant (**PRA**), Nathan DeJong who then enrolled in Grad School at the Colorado State University in September 2016. During this period, I completed a number of trainings offered by the University of Colorado and the NIH to learn how to efficiently manage a lab including Lab Management, Budget Management, Team Building and Leadership Development, Scientific and Technical Writing and Career development Workshops.

I was recruited at the CNRS as a permanent researcher in January 2016. To maintain the research program I initiated at the University of Colorado, I created a Joint International Lab (LIA ACTIMOVE) between the IPHC CNRS (**Error! Reference source not found.**) and the Division of Endocrinology, Anschutz Health & Wellness Center at the University of Colorado (**Photo 4**), which are research institutions recognized for their research excellence in ecology and eco-physiology, and medicine. The objective was to develop a research program to understand the overall transition of physical activity and its impact on health, and develop strategies of prevention of sedentary behaviors and the associated chronic diseases. The project is based on a unique interdisciplinary approach using a health ecology perspective that put together physicians, physiologists and ecologists. This is a novel and innovative management project of a conflict between environment and health that is organized in three axes of research going from observation to experimentation, and implementation of new strategies of prevention of sedentary behaviors. These strategies will be tested in the future in free-living conditions using a unique socio-ecological approach (project that has not started and was not developed in this manuscript). Researchers who are participating in the LIA at the University of Colorado include Drs James O. Hill (until December 2018, now at University of Birmingham Alabama), Daniel Bessesen, Paul MacLean and Edward Melanson. I have also hired three PRAs who have helped coordinating the study protocols. The research program has been approved for a first 5-year period (renewable). Research is being conducted in France and the State of Colorado in the United States but also in Senegal (under the tutelage of France, Observatoire Hommes-Milieux International (OHM) Tessekéré (Labex DRIIHM: http://www.driihm.fr/) as described in the section 23 of the research activities description.

In 2017, I took the lead of a new team in the Department of Ecology, Physiology and Ethology (**DEPE**). The "Physiological Adaptations to Gravity & Health" (**PAGRAS**) team is composed of a Director of Research (S Blanc), two Research Scientists (including me), an engineer (IE, A Zahariev), an engineer assistant (AI, I Chery), two post-doctoral fellows (C Laurens and E Cohen) and until December 2018 we had a doctoral student (A Damiot). Two new PhD students (P Bourdier and E Le Roux) will join us starting October 2019. This team is characterized by its interdisciplinary dimension. We bring together expertise in integrated physiology, cell and molecular biology, cultural bio-anthropology, organic and physical chemistry. In addition to its research activities, the team possesses a mass spectrometry platform dedicated to the study of energy metabolism and nutrients in animals and humans. It is used for our own research projects, but also for the projects of other DEPE teams and national and international collaborators. Our research activities are detailed on this website: http://www.iphc.cnrs.fr/-adaptations-Physiologiques-A-la-GRAvite-Sante-PAGRAS-.html.

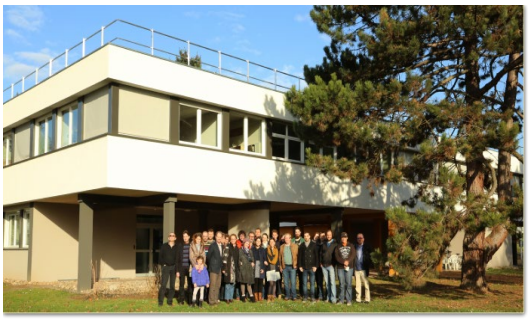

PHOTO 3 : CNRS IPHC – DEPE

Photo 4 : University of Colorado – Anschutz Medical Campus

COMMUNITY AND SERVICE ACTIVITIES

During my post-doctorate fellowship at the University of Colorado, I was leading the Post-Doctoral Association of the Anschutz Health and Wellness Center (2012-2016).

Upon my recruitment at the CNRS, I accepted to be a member of the IPHC Animal Welfare Bureau, which ensures the living, treatment and experimental conditions of the animals kept in the laboratory (2016-2018). Recently I have volunteered to join the IPHC Scientific Council (2020-2024), first meeting will be in November.

Since January 2019, I have been appointed to the Scientific Programs Council of the CNES. This year we mainly focused on the CNES prospects for the next five years that will be presented in October. I am also a member of the Topical Team organized and supported by ESA on the following topics: "Nutrition & Metabolism" and "Aging and Space". The purpose of these committees is to synthesize current knowledge into a review and define future research priorities for space science and human space flights.

As part of the LIA with the University of Colorado, I was appointed in Spring 2019 to be an expert member of the Steering Committee of the Mass Spectrometry Core dedicated to the measurement of TEE and body composition using the DLW method.

I finally take an increasing role in editorial activities. Since 2018, I have been a reviewer editor of Frontiers in Physiology: Environmental, Aviation & Space Physiology Section. In 2019, I was selected to serve on the editorial board of the Journal of Physiology, and I have recently joined the editorial board of Frontiers in Nutrition: Nutrition & Metabolism. Since 2016, I have been reviewing an increasing number of articles, between 15 and 20 articles per year, for leading journals in the fields of research on obesity, metabolism, physiology, exercise and physical activity, nutrition, space and public health (see list of journals in the CV). Prestigious journals such as Diabetes, Journal of Clinical Endocrinology, Journal of Physiology and Endocrine Reviews asked for my expertise. I have been reviewing abstracts for The Obesity Society's annual conference every year for the past three years. Finally, funding institutes such as the European Science Foundation, the Leakey Foundation, the NIH, the Colorado Clinical Translational & Scientific Institute at the University of Colorado asked me to evaluate research projects.

MENTORING ACTIVITIES

Over the past 10 years, I have been directly involved in mentoring a broad range of scientists at every stage of professional development, including 10 undergraduate/Masters' students, 4 PhD graduate students and 2 post-doctoral fellows. Those who completed their training have successfully moved on to Nursing, Medical and Graduate schools, Post-doctoral fellowships and Faculty position in academia. My students received a number of awards, prizes and recognitions (See details in CV). I am an affiliated mentor of the CCTSI TL1 program and of the T32 institutional training program in Endocrinology, Metabolism and Diabetes at the University of Colorado in the context of the LIA. I have also served on several advisory, Masters and PhD thesis committees.

To improve my mentoring skills, I completed the 2017 Junior Faculty Mentor Program hosted by the CCTSI at the University of Colorado and the 2018 Colorado Mentoring Training Program. These workshops aim to address the unique challenges that junior scientists are faced with when they are asked by students and fellows to assume a mentoring role.

Finally, I organize a multi-site meeting for graduate students and post-doctoral fellows which meets monthly through video conference and includes members and Faculty members from France (IPHC-CNRS and CNRH Lyon), Ireland (DCU), Australia (Baker IDI) and the US (University of Colorado). This meeting is fully dedicated to the training of mentees with oral presentations on specific topics related to respective research projects, reviews of scientific papers and journal clubs.

RESEARCH CULTURE PROMOTION

I am dedicated to promoting research culture among the general population and the younger generations. In this line, I have contributed to several book chapters, and wrote articles and blogs on the Internet for the lay audience (see details in CV).

I regularly volunteer to give oral presentations to the general community. I have done it every other years at the Museum of Natural History and Science in Denver, Colorado and at the Café Scientifique of the Alliance Française in Denver. I have also given interventions in high schools and public libraries on diverse scientific topics, including the anniversary of Marie Curie, Nutrition in Space, Challenges of the Life in Space, The adverse health effects of sitting, the adaptations of the body to an Arctic expedition, etc.

My research work also receives regular media attention. The bed rest studies as well as the study conducted on the ISS are often covered by the local and national press, radio or TV (ActuToulouse, La Croix, La Manche Libre, La Dépêche, Sciences & Vie, MyAlsace, France Info, NewsBeezer, 20 minutes, Le Parisien, Dernières Nouvelles d'Alsace, L'Alsace, Ouest France, etc). Often these articles are then relayed on many national and international websites. Most of the time I accept to participate in interviews with journalists and thus hope to attract interest of the general population to science and help them changing their lifestyle to improve their health. Recently, I talked about my research on physical inactivity on RCF in Strasbourg in March 2019 (Eureka radio show) as part of the month "A vélo au travail" (Bike to Work).

Finally, the POWER study on women who have reached the North Pole on skis is the subject of a documentary film "EXPOSURE" directed by Holly Morris, a well-known American documentary filmmaker/producer. The research we carried out as part of this expedition is largely covered in the documentary that will be shown at adventure festivals around the world from 2020. This study was also reported in 2018 in international newspapers such as Wired, Outside, or Global Sports Matters.

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ANNEX: EXHAUSTIVE LIST OF SUBMITTED PROPOSALS

Total number of applications: 59; Number of applications granted: 25; Succes rate: 43%; Total amount of funding: 1.8M€

Funding Call	Year	PI	Role	Topic	Amount	Status
NIH NIDDK F31 pre-doctoral fellowship award	2019	N. Delong	Mentor	A mechanistic study to understand the beneficial effects of breaking up sedentary behaviors on glycemic control	90k USD	Pending
CNES	2019	A. Bergouignan	PI	CONSEQUENCES OF 5 DAYS OF DRY IMMERSION ON WHOLE-BODY METABOLIC FLEXIBILITY, SKELETAL MUSCLE ENERGY METABOLISM, INSULIN SENSITIVITY AND MUSCLE-BONE TALK	34k	Pending
Diabetes Research Center - University of Colorado	2019	A. Bergouignan	PI	WHY SPREADING SHORT BOUTS OF ACTIVITY THROUGHOUT THE DAY HAS MORE BENEFICIAL EFFECTS ON GLUCOSE HOMEOSTASIS THAN PERFORMING A CONTINUOUS BOUT OF ACTIVITY? A pilot study to identify the potential exerkines associated with these differential effects	100k USD	Pending
ESA	2019	A. Bergouignan	PI	Revisiting the exercise countermeasure to prevent the microgravity-induced adverse health outcomes without inducing energy deficit: A pre-requesite study for planetary exploration	OK (grant access to the astronauts)	Pending
CNRS GDR Sport et Santé	2019	A. Bergouignan	Mentor	Fragmenter le temps passé assis : Une nouvelle stratégie d'activité physique au-delà de la pratique d'un sport pour la santé métabolique	100k€	Granted
Société Française de Nutrition	2019	A. Bergouignan	PI	Etudier la transition épidémiologique dans une population pastoraliste nomade pour comprendre l'impact des changements du régime alimentaire et l'activité physique sur la régulation du poids.	20k€	Granted
ANR	2019	S. Blanc	Co-PI	TRANSITION: Epidemiological transition in Fulani nomad pastoralists in Senegal: Impact of sedentarization on lifestyle, diet, physical activities and body weight	1.2M€	Pre-selected; Rejected
Bourse Châteaubriand	2019	N. Delong	Mentor	Effect of frequent interruptions of sedentray behaviors on lipid metabolism	25k€	Rejected
IRESP	2019	A. Bergouignan	PI	A multi-level intervention to prevent sedentary behavior-induced adverse health outcomes in office workers	250k€	Rejected
NIH NIDDK R01 award	2019	A. Bergouignan	PI	Sit less, move more: Establishing the biological mechanisms supporting the new consensus-based and non-prescriptive guidelines to prevent type 2 diabetes against sedentary behaviors	3.5M USD	Rejected
CNES	2018	S. Blanc	Co-I	ENERGY: Role of spontaneous physical activity in the regulation of energy balance in the astronauts during long-term space missions	20k€	Granted
CNES	2018	A. Bergouignan	PI	Short-term effects of dry immersion on muscle myokines and muscle nutrient metabolism in young healthy males	30k€	Granted
CNES	2018	S. Blanc	Co-I	Functional and metabolic consequences of ectopic fat storage during bed rest: A mechanistic and kinetic approach for testing an anti-oxidant/anti-inflammatory dietary mix as nutrition countermeasure	50k€	Granted
ANR	2018	C. Gilbert	Co-I	DIVHYPO: DIVing into physiological paradoxes: HYPOxemia and hypothermia in foraging seals	400k€	Rejected
ANR	2018	F. Criscuolo	Co-I	AGEs: Are Birds demigods of glycation Resistance?	580k€	Rejected
ANR	2018	J.Y. Georges	Co-I	SMARTPOP: Swifts, Migration And Responses To POP	522k€	Rejected
ANR	2018	S. Blanc	Co-I	TRANSITION: Epidemiological transition in Fulani nomad pastoralists in Senegal: Impact of sedentarization on lifestyle, diet, physical activities and body weight	1.2M€	Pre-selected; Short listed
CNRS LabEX DRIIHM Post-doctoral Fellowship	2018	S. Blanc	Co-I	Epidemiological transition in Fulani nomad pastoralists in Senegal: Impact of sedentarization on life style, diet, physical activities and weight.	40k€	Granted
CNRS Mission Interdisciplinaire	2018	A. Bergouignan	PI	Testing evolutionary medicine concepts: Is total energy expenditure homeostatically regulated in humans?	30k€	Granted
NASA	2018	A. Bergouignan	PI	Fit, fat and fat-free: a re-evaluation of the exercise countermeasure in the long-term control of energy balance in astronauts. A pre-requisite study for planetary exploration	250k€	Rejected
NIH CCTSI Junior Co-Pilot Award	2018	A. Bergouignan	PI	Effect of frequent interruptions of sedentary time on glucose homeostasis in free-living prediabetic overweight adults	30k USD	Granted
NIH CCTSI TTDS TL1 pre-doctoral fellowship	2018	N. Delong	Mentor	Metabolic effects of breaking up sedentary time	40k USD	Granted
NIH Director's New Innovator Award Program	2018	A. Bergouignan	PI	Study of the epidemiological transition in Fulani nomad pastoralists in Senegal to understand the socio-ecological drivers of body weight gain and associated metabolic	1.5M USD	Rejected
NIH NIDDK F31 pre-doctoral fellowship award	2018	N. Delong	Mentor	Effect of breaking-up sedentary behaviors on nutrient metabolism and insulin sensitivity: an integrative approach	124k USD	Pending
Prix de recherche IDF - FRM pour les sciences de l'alimentation	2018	S. Blanc	Co-I	Epidemiological transition in Fulani nomad pastoralists in Senegal: Impact of sedentarization on life style, diet, physical activities and weight.	40k€	Granted
ANR	2017	F. Criscuolo	Co-I	SAFE: Screening Ants For Eternity	387k€	Rejected
ANR	2017	C. Gilbert	Co-I	"Pace of life Syndrome" in elephant seals: life cycle energetic strategies and personality	390k€	Rejected
ANR JCJC	2017	A. Bergouignan	PI	Breaking up prolonged sedentary time: a novel strategy to improve metabolic health	244.7k€	Pre-selected; rejected
Australian Victoria Fellowshis	2017	M. Grace	Mentor	Sit less, move more: Determining potential mechanisms which underlie the health benefits of breaking up prolonged sitting	40k AUSD	Rejected
CNES	2017	A. Bergouignan	PI	Short-term effects of dry immersion on metabolic flexibility in young healthy males	50k€	Granted
CNRS Défi AUTON	2017	C. Sueur	Co-I	Approche socio-écolgique des personnes âgées fragilisées à domicile: étude des effets des dispositifs technologiques sur l'autonomie	30k€	Rejected
CNRS INEE Laboratoire International Associé	2017	A. Bergouignan	PI	ACTIMOVE: The global transition of physical activity: Management of a conflict between environment and health	50k€	Granted
National Geographic	2017	A. Bergouignan	PI	POWER study - Physiological adaptations in women during a North Pole exploration	50k€	Rejected
NIH CCTSI TTDS TL1 pre-doctoral fellowship	2017	N. Delong	Mentor	Breaking up prolonged sedentary time to improve metabolic health	40k USD	Rejected
NIH NIDDK R01 award	2017	J.O. Hill	Collaborator	Matching diet to metabolism to prevent weight regain in individuals with prediabetes.	3.7M USD	Rejected
ACSM Odeil Bar-Or International Scholar Award	2016	N. Delong	Mentor	The energetics of breaking up sedentary behavior	10k USD	Rejected
CNRS INEE PEPS Blanc	2016	A. Bergouignan	PI	What do the brown bear and European hamster are dreaming about? Study of the role of arousal episodes during hibernation	15k€	Granted
CCTSI Mentored Pilot Study Award	2016	A. Bergouignan	PI	Neuronal depictions of sedentary activities and exercise	20k USD	Rejected
Colorado School of Public Health, MAP ERC, Occupational & Environmental Health & Safety award	2016	A. Bergouignan	PI	Microbouts of activity to combat sitting disease in office workers	15k USD	Granted
NORC Young Investigator Award	2016	A. Bergouignan	PI	Neuronal depictions of sedentary activities and exercise	30k USD	Rejected
Université de Strasbourg IdEX	2016	A. Bergouignan	PI	Breaking up prolonged sedentary time: a novel strategy to improve metabolic health	352k€	Rejected
CCTSI Microgrant	2016	A. Bergouignan	PI	Effects of microbouts of activity on metabolic health.	20k USD	Granted
University of Colorado, Division of Endocrinology	2016	A. Bergouignan	PI	Effects of microbouts of activity on metabolic health.	300k USD	Granted
CNES	2015	S. Blanc	Co-I	A dietary anti-oxidant cocktail supplementation as a new countermeasure against musculo-skeletal system and metabolic alterations induced by physical inactivity in	50k€	Granted
CCTSI Mentored Pilot Study Award	2015	A. Bergouignan	PI	Neuronal depictions of sedentary activities and exercise	20k USD	Rejected
NIH BEST Visitor Scientist Aard	2015	A. Bergouignan	PI	Effect of breaking up sedentary behavior on adipose tissue biology	5k USD	Granted
University of Colorado, School of Medicine	2015	A. Bergouignan	PI	Breaking-up prolonged sitting to offset sedentary behaviors-induced metabolic alterations.	25k USD	Granted
NIH/NIDDK K99/R00 Pathway to the Independence Award - Equivalent to ERC Starting Grant	2014	A. Bergouignan	PI	Breaking-up prolonged sitting to offset sedentary behaviors-induced metabolic alterations.	925k USD	Granted
CCTSI Microgrant	2014	A. Bergouignan	PI	Breaking-up prolonged sitting to offset sedentary behaviors-induced metabolic alterations.	20kUSD	Granted
Australian Government Endeavour Postgraduate Research Fellowship	2013	A. Bergouignan	PI	Effect of frequent breaks-up of prolonged sitting on metabolic flexibility.	25k AUSD	Granted
Johnson & Johnson Company	2013	J.O. Hill	Collaborator	Effect of microbouts of physical activity on cognitive functions and metabolism.	100k USD	Granted
Wellcome Trust Fellowship	2013	A. Bergouignan	PI	Breaking-up prolonged sitting to offset sedentary behaviors-induced metabolic alterations.	696k€	Rejected
ADA Mentored-Based Postdoctoral Fellowship	2011	D. Bessesen	Post-doc	Dietary fat oxidation and trafficking in obesity and reduced-obesity.	177k USD	Rejected
CCTSI Mentored Pilot Study Award	2011	A. Bergouignan	PI	A novel tracer method to understand the mechanisms of reduced dietary fat oxidation in obese and reduced-obese humans.	20k USD	Granted
NORC Young Investigator Award	2011	A. Bergouignan	PI	Dietary fat oxidation and trafficking in obesity and reduced-obesity.	30k USD	Granted
CCTSI Mentored Pilot Study Award	2009	A. Bergouignan	PI	Effect of a short-term high-fat diet on fasting and post-prandial inflammatory markers in lean trained, lean sedentary and obese sedentary individuals	20k USD	Rejected
EFSD and Lilly Grant	2009	S. Blanc	Co-I	Effect of contrasted changes in non-exercise physical activity on dietary lipid metabolism and insulin sensitivity: Inferences on the role of activities of daily living in the etiology and prevention of insulin resistance	100k€	Rejected
Marie Curie International Outgoing Fellowship	2009	A. Bergouignan	PI	NEPAFOX: Effect of contrasted changes in non-exercise physical activity on dietary lipid trafficking and insulin sensitivity: Role of lifestyle in etiology/prevention/treatment of obesity and diabetes	230k€	Rejected
The Life Sciences Research Foundation	2009	A. Bergouignan	PI	Impact of activities of daily life on insulin sensitivity and dietary fat metabolism	100k USD	Rejected
DSM Award	2008	A. Bergouignan	PI	Effect of physical inactivity on energy and oxidative balances in women	10k€	Rejected

ADA, American Diabetes Association; ANR, Agence Nationale de la Recherche; CNES, Centre National des Etudes Spatiales; CCTSI, Colorado Clinical Translational and Scientific Institute; CNRS, Centre National de la Recherche Scientifique; EFSD, European Foundation or the Study of Diabetes; FRM, Fondation de la Recherche Médicale; INEE, Institut National de l'Ecologie et de l'Environnement; IRESP, Institut de Recherche en Santé Publique; NASA, National American Space Agency; NIH, National Institute for Health; NIDDK, National Institute of Digestive, Diabetes and Kidney diseases; NORC, National Obesity Research Center; PEPS, Projet Exploratoire et de Premier Soutien

RESUME EN FRANÇAIS

La compréhension de nombreux problèmes de santé modernes ne peut se faire en dehors d'une approche évolutive et écologique. L'approche évolutive reconnait les contraintes biologiques imposées par le fait que la plus grande part de l'évolution humaine a eu lieu alors que nos ancêtres étaient des chasseurs-cueilleurs. En effet, 95% de la biologie humaine, et probablement des comportements humains, ont été naturellement sélectionnés au moment de l'émergence du génome humain moderne avec l'apparition de l'Homo sapiens il y a environ 200 000 ans. Depuis, notre patrimoine génétique bien qu'en constante évolution, aurait subi peu de mutations et serait resté relativement stable pour ce qui concerne notre physiologie. Bien que les gènes jouent un rôle dans la régulation du métabolisme chez l'homme via la susceptibilité individuelle, ils ne peuvent à eux seuls expliquer l'évolution récente des maladies non transmissibles dont la prévalence augmente. L'approche écologique reconnaît dans ce contexte l'importance des facteurs environnementaux dans la genèse des pathologies modernes. Les facteurs environnementaux qui divergent de ceux de nos ancêtres sont spécifiquement liés à nos modes de vie et notamment aux comportements alimentaires et de mouvement (activité physique). Les populations occidentales ou ayant terminé leur transition épidémiologique ont largement adopté les comportements sédentaires et sont principalement inactifs. L'inactivité physique a été reconnue comme un problème majeur de santé publique par l'OMS et The Lancet en Juillet 2012 dans lequel a été écrit: « De par sa prévalence, sa large distribution géographique et ses effets sur la santé, l'inactivité physique doit être reconnue comme une pandémie qui a des conséquences importantes de santé, environnementales, sociétales et économiques ». Cette déclaration a été réitérée et renforcée dans un nouveau numéro spécial du Lancet en Juillet 2016.

Dans ce contexte alarmant, les objectifs principaux de mon programme de recherche sont (i) de comprendre le rôle de l'inactivité physique et des comportements sédentaires dans l'émergence des maladies métaboliques, comme l'obésité, l'insulinorésistance et le diabète de type 2, et (ii) de développer des stratégies novatrices qui peuvent prévenir les effets délétères de l'inactivité physique et des comportements sédentaires. Le but ultime est d'apporter des données solides, fortes et irréfutables sur les méfaits de la sédentarité et les stratégies pouvant les prévenir afin d'aider au développement de futures initiatives de santé publique, et de convaincre les acteurs politiques de la nécessité de considérer la sédentarité comme un problème de santé majeur qui nécessite d'être vaincu.

Mon approche scientifique combine des modèles et des paradigmes uniques dans des environnements extrêmes et dans la vie réelle pour comprendre la physiopathologie des comportements sédentaires et de l'inactivité physique. Au cours d'études expérimentales et d'intervention notamment dans des milieux aux conditions extrêmes (ex : environnement spatial simulé ou vrai), je cherche à caractériser les mécanismes sous-jacents. Les études menées dans la vie réelle visent à confirmer les résultats observés dans ces conditions extrêmes. Pour l'ensemble de ces études, j'utilise une approche sophistiquée de physiologie intégrative qui étudie les réponses métaboliques à différents niveaux d'intégration allant du corps entier aux niveaux des organes, des cellules, des protéines et des gènes. Ma recherche vise spécifiquement à déterminer les effets des comportements sédentaires sur les paramètres clés impliqués dans la régulation du poids corporel et de la santé métabolique, comme la flexibilité métabolique. La flexibilité métabolique, définie comme la capacité d'ajuster l'utilisation des substrats aux changements de leur disponibilité et de la demande, est considérée comme une composante essentielle de la santé métabolique. Je cherche également à tester l'efficacité de nouvelles stratégies (alimentation ou activité physique) pour prévenir les effets indésirables sur la santé des comportements sédentaires. Enfin je m'intéresse à comprendre comment les différentes composantes de la balance énergétique (le résultat entre l'apport et la dépense énergétique), interagissent entre elles et régulent le poids corporel. En adoptant une approche socio-éco-physiologique, je cherche à comprendre le rôle respectif des facteurs biologiques, environnementaux, sociologiques et anthropologiques (style de vie/culture) dans la régulation du poids corporel et la santé métabolique.

Dans ce manuscrit, je résume mon parcours professionnel depuis ma thèse, mon expérience au cours de ces 15 années de recherche passées, les résultats et faits marquants ainsi que les futurs projets que j'envisage de mener. Je décris également mon rôle et mon implication dans la gestion de la recherche, la recherche de financements, et la supervision d'étudiants et de post-doctorants. Enfin, je décris les activités collectives dans lesquelles je m'implique ainsi que celles qui vont au-delà de mes tâches professionnelles et qui cherchent à partager ma passion des sciences et de la recherche avec la population générale et les jeunes générations. J'espère ainsi pouvoir contribuer à aider chacun à améliorer son mode de vie et sa santé mais aussi à créer des vocations pour les métiers de la recherche.