BIOGRAPHICAL SKETCH

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NAME: **Johan AUWERX, M.D., Ph.D.**

eRA COMMONS USER NAME (credential, e.g., agency login): **AUWERX**

POSITION TITLE: **Professor** at the Ecole Polytechnique Fédérale Lausanne (EPFL), Switzerland

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	COMPLETION DATE	FIELD OF STUDY
Catholic University of Leuven, Leuven, Belgium	B.S.	1979	Biochemistry & Genetics
Catholic University of Leuven, Leuven, Belgium	M.D.	1982	Medicine
Catholic University of Leuven, Leuven, Belgium	Resident	1982-1986	Intern. Med/Endocrinology
Catholic University of Leuven, Leuven, Belgium	Ph.D.	1990	Molecular Endocrinology
University of Washington, Seattle, WA	Post-doc	1986-1988	Molecular Endocrinology
ECFMG / VQE	M.D.	1982	

A. Personal Statement

I am trained as a physician scientist and have extensive research expertise and experience in cellular and molecular physiology, metabolism, and genetics developed in *C. elegans*, mice, and humans. I have been using systems approaches to map the signaling networks that coordinate the communication between the nucleus and the mitochondria and as such regulate organismal metabolism in health, aging, and disease. Although my research has addressed basic biomedical questions, my medical background facilitated the translation of his research into novel preventive and therapeutic strategies for common age-related diseases, such as type 2 diabetes, obesity, atherosclerosis, and frailty, as well as for rare inherited mitochondrial diseases. The translational value of my work is testified by the fact that several drugs targeting processes and pathways, which I elucidated are currently used in the clinic.

B. Positions and Honors

POSITIONS AND EMPLOYMENT:

1986-1988 Research Fellow, Div. of Metabolism and Med. Genetics, University of Washington, Seattle, WA.
1988-1991 Research Associate of the National Fund for Scientific Research, University of Leuven, Belgium.
1991-2003 Research Director CNRS (DR1; ~ to Full Professor), since 1999 at the IGBMC, Illkirch, France.
2003-2008 Professor of Medicine (PU-PH), Université Louis Pasteur (ULP), Strasbourg, France
2006-2008 Director, Institut Clinique de la Souris, Illkirch, France
2008- Professor, Ecole Polytechnique Fédérale, Lausanne, Switzerland

HONORS AND AWARDS:

Horlait-Dapsens Prize for Medical Research, Belgium, 1985; Fullbright Award, USA, 1986; J.Fogarty International Research Fellowship (NIH), USA, 1987-88; ILSI award, USA, 1989; F. De Waele Prize for Cancer Research, Belgium, 1989; Morgagni Young Investigator Award, Italy, 1989; Boehringer Prize for Atherosclerosis, Belgium, 1989; Belgian Endocrine Society Award, Belgium, 1992; Prix Danone "Santé et Nutrition", France, 1992; Prix de la Fondation pour la Recherche Médicale, France, 1998; Minkowski Prize, European Association for the Study of Diabetes, EU, 1998; Spa Prize for Nutrition, Belgium, 1998; EMBO member 2003; Morgagni Gold Medal, Italy, 2004; Jean Valade Prize of the Fondation de France, France, 2005; Josiah Brown Lecture Award, CA, 2006; Ruysch Lecture, AMC Amsterdam, Netherlands, 2008; Danone International Prize for Nutrition, France, 2009; Hans Popper Lecture Award of the American Association for the Study of Liver Disease, USA, 2010; Adolf Windaus Prize, Falk Foundation, Germany, 2010; Jacobeus Lecture Award, Nordic countries, 2011; Paul F. Glenn Lecture, Massachusetts Institute of Technology, USA, 2013; Umesono Memorial Lecture, The Salk Institute, USA, 2013; Ruth Okey Lecture, UC Berkeley, CA; USA, 2013; Nutrition & Sante Prize, France, 2013; The Biomedicum Helsinki Lecture, Finland, 2013; Doctor Honoris

Causa, Université Blaise Pascal, Clermont-Ferrand; France, 2013; The Marcel Benoist Prize, Switzerland, 2016; The Journal of Lipid Research lecture, Duel Conference, Monterrey, CA, USA, 2017; 5th Helmholtz-Nature Medicine Diabetes Lecture, Munchen, Germany, 2017

BOARD AND SOCIETY MEMBERSHIPS:

- Elected Member of the European Molecular Biology Organization in 2003.

- Editorial Boards: Annals of Medicine (2001-), Journal of Clinical Endocrinology Metabolism (2002-05), Molecular Endocrinology (2003-07), Endocrine Reviews (2008-11), Cell Metabolism (2004-), The EMBO Journal (2008-20), EMBO reports (2008-12), Cell (2008-2020), Mammalian Genome (2011-), Science (2011-), Aging Cell (2013-18), Molecular Systems Biology (2014-), and Journal of Cell Biology (2015-).

- Scientific Advisory Board - academic: European Research Institute for the Biology of Aging (ERIBA), Groningen, NL (2011-); Novo-Nordisk Foundation Center for Basic Metabolic Research, Copenhagen, DK (2012-17); The Morgridge Institute, University of Wisconsin, Madison, WI (2013-14); Center for Epigenetics and Metabolism, University of California, Irvine, CA (2012-20).

- Scientific Advisory Board and/or consultancy - private: Ligand Pharmaceuticals, San Diego, CA (1995-2001); CareX, Illkirch, FR (2001-04); Sirtris, Waltham, MA (2004-08); PhytoDia, Illkirch, FR (2006-); Intercept Pharmaceuticals, NY, NY (2007-10); Lombard-Odier Bank, Geneva, CH (2009-12): Amazentis, Lausanne, CH (2009-); Merck Research Laboratories, Rahway, NJ (2009-13); Mitobridge - Astellas, Cambridge, MA (2013-); TES Pharma, Corciano, IT (2016-); Janssen Pharmaceuticals, Springhouse, PA (2017-); NOV Metapharma, Seoul, KR (2019-); The Liver Company, Stanford, CA (2020-); Altissimo, Cambridge, MA (2020-).

- Chairman ERC Advanced Grants Life Sciences Panel 4 – cancer, physiology, and endocrinology (2009-15).

- Member of the EMBO Membership/Nomination Committee (2015-18).

C. Contributions to Science

My work has been focused on the mapping of signaling networks and pathways that govern mitochondrial function and as such regulate organismal metabolism. My research has allowed the development of new methodologies and scientific approaches (see under #1), but also contributed to improved understanding of how the communication between the mitochondria and nucleus controls mitochondrial function and metabolism (see under #2-5), leading to the development of new treatments for metabolic dysfunction.

My work is highly cited (https://hcr.clarivate.com/#freeText%3Dauwerx) and my current h-index (ISI- Web of Science) is 139 (total number of citations is >73'000 with ~106 citations / article). A full list of publication is at: http://www.ncbi.nlm.nih.gov/pubmed/?term=auwerx

(#1) I have been at the forefront of **systems, integrative, and multi-layered approaches** to map the signaling networks and pathways that govern metabolism. My team has pioneered a unique and powerful cross-species genetic and multi-layered 'omics gene discovery pipeline using cellular models, *C.elegans*, genetically engineered mouse models (GEMMs), mouse genetic reference populations (GRPs, such as the BXD strains), and human cohorts. This approach provided new and effective ways to identify and validate candidate genes and pathways involved in metabolic control with high clinical translational value.

P.A. Andreux, E.G. Williams, H. Koutnikova, R.H. Houtkooper, M.F. Champy, H. Henry, K. Schoonjans, R.W. Williams, J. Auwerx. Systems genetics of metabolism – the use of the BXD murine reference panel for multiscalar integration of traits. Cell 2012, 150, 1287-1299. PMC3604687

Y. Wu, E.G. Williams, S. Dubuis, A. Mottis, V. Jovaisaite, S.M. Houten, C.A. Argmann, P. Faridi, W. Wolski, Z. Kutalik, N. Zamboni, J. Auwerx*, R. Aebersold* (*co-corresponding authors). Multilayered genetic and omics dissection of mitochondrial activity in a mouse genetic reference population. Cell, 2014, 158, 1415-1430. PMC4179868

E.G. Williams, Y. Wu, S. Dubuis, P. Blattmann, C. Argmann, S. Houten, T. Amariuta, W. Wolski, N. Zamboni, R. Aebersold*, J. Auwerx*. (*co-corresponding authors) Systems proteomics and trans-omic integration illuminate new mechanisms in mitochondrial function. Science, 2016, 352, aad0189 - DOI: 10.1126/science.aad0189. PMID27284200

H. Li, X. Wang, D. Rukina, Q. Huang, T. Lin, V. Sorrentino, H. Zhang, M. Bou Sleiman, D. Arends, A. McDaid, P. Luan, N. Ziari, L.A. Velázquez-Villegas, K. Gariani, Z. Kutalik, K. Schoonjans, R.A. Radcliffe, P. Prins, S. Morgenthaler, R.W. Williams, J. Auwerx. An integrated systems genetics and omics toolkit to probe gene function. Cell Systems, 2018, 2018, 6, 90-102.e4. PMID29199021

(#2) My work was instrumental to establish that many receptors—both **membrane and nuclear receptors**—act as sensors that capture changes in the cellular energy status and that translate this information into altered nuclear gene expression patterns affecting mitochondrial function and metabolism. These pathways constitute an essential aspect of the antegrade control of mitochondrial activity, i.e. nucleus→mitochondria. I was amongst the pioneers to unravel the wide-ranging implications of the **PPARs** (α, β/δ, and γ) and the enterohepatic nuclear receptors—LRH-1 and SHP—in metabolic control. My discovery of the association between the PPARγ Pro12Ala gene variant with type 2 diabetes and obesity, long before the era of genome-wide association studies, was the first identification of a gene tied with common complex diseases. Our discovery that bile acids act as endocrine regulators of energy expenditure, glucose homeostasis, inflammation, and atherosclerosis, through the activation of the membrane bile acid receptor, **TGR5**, sparked a paradigm shift that transformed bile acids from lipid solubilizers in the gut to versatile endocrine signals that impact almost every aspect of metabolism.

K. Schoonjans, J. Peinado-Onsurbe, A.-M. Lefebvre, R. A. Heyman, M. Briggs, S. Deeb, B. Staels, J. Auwerx. PPARα and PPARγ activators direct a distinct transcriptional response via a PPRE in the lipoprotein lipase gene. EMBO J. 1996, 15, 5336-48. PMC452277

S.S. Deeb, L. Fajas, M. Nemoto, M. Laakso, W. Fujimoto, J. Auwerx. A Pro12Ala substitution in the human PPARγ2 gene associated with decreased receptor activity, lower BMI and improved insulin sensitivity. Nat. Genet., 1998, 20, 284-7. PMID9806549

M. Watanabe, S.M. Houten, C. Mataki, M.A. Christoffolete, B.W. Kim, H. Sato, N. Messaddeq, J.W. Harney, O. Ezaki, T. Kodama, K. Schoonjans, A.C. Bianco, J. Auwerx. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. Nature, 2006, 439, 484-9. PMID16400329

C. Thomas, A. Gioiello, L. Noriega, A. Strehle, J. Oury, G. Rizzo, A. Machiarullo, H. Yamamoto, C. Mataki, M. Pruzanski, R. Pelliciari, J.Auwerx, K. Schoonjans. TGR5-mediated bile acid sensing controls glucose homeostasis. Cell Metabolism, 2009, 167-177. PMC2739652

(#3) Later we showed that not only transcription factors but also several **transcriptional coregulators** were important in the antegrade control of mitochondrial function. In fact, we established that a yin-yang between transcriptional corepressors—NCoR1 and the sirtuin deacetylases (see also below in point #4)—and coactivators—PGC-1α and the steroid receptor coactivators— fine-tunes oxidative metabolism.

M. Lagouge, C. Argmann, Z. Gerhart-Hines, H. Meziane, C. Lerin, F. Daussin, N. Messadeq, J. Milne, P. Lambert, P. Elliot, B. Geny, M. Laakso, P. Puigserver, J. Auwerx. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1α. Cell , 2006, 127, 1109-1122. PMID17112576

H. Yamamoto, E.G. Williams, L. Mouchiroud, C. Canto, W. Fan, M. Downes, C. Heligon, G.D. Barish, B. Desvergne, R.M. Evans, K. Schoonjans, J. Auwerx. NCoR1 is a conserved physiological modulator of muscle mass and oxidative function. Cell, 2011, 147, 827-839. PMC3225739

P. Bai, C. Canto, H. Oudart, A. Brunyánszki, Y. Cen, C. Thomas, H. Yamamoto, A. Huber, B. Kiss, R.H. Houtkooper, K. Schoonjans, V. Schreiber, A.A. Sauve, J. Menissier-de Murcia, J. Auwerx PARP-1 inhibition increases mitochondrial metabolism through SIRT1 activation. Cell Metabolism, 2011, 13, 461-468. PMC3086520

D. Ryu, Y.-S. Jo, G. Lo Sasso, S. Stein, H. Zhang, A. Perino, J.U. Lee, M. Zeviani, R. Romand, M.O. Hottiger, K. Schoonjans, J. Auwerx. A Sirt7-dependent acetylation switch of GABPbeta1 controls mitochondrial function. Cell Metabolism, 2014, 20, 856-869. PMID25200183

(#4) Our team was involved in the discovery that many transcriptional coregulator networks, in particular that governed by the sirtuins, convert signals associated with cellular energy status—such as **NAD^+** and ATP levels—into altered transcriptional output to govern mitochondrial function and metabolism. This discovery not only attributes an important signaling role to the sirtuin coregulator family, but more importantly transforms NAD^+ from its classic function as a cofactor for redox reactions into an active signaling factor. This work also indicated that replenishing cellular NAD^+ stores is an effective strategy to treat diseases that are characterized by defective NAD^+ homeostasis and to enhance health- and lifespan (see also under #5).

C. Canto, Z. Gerhart-Hines, J.N. Feige, M. Lagouge, L. Noriega, J.C. Millne, P. Puigserver, J. Auwerx. AMPK regulates energy expenditure by modulating NAD+ metabolism and SIRT1 activity. Nature, 2009, 458, 1056-1060. PMC3616311

C. Canto, R.H. Houtkooper, E. Pirinen, D.Y. Youn, M.H. Oosterveer, P.J. Fernandez-Marcos, H. Yamamoto, P.A. Andreux, P. Cettour-Rose, K. Gademann, C. Rinsch, K. Schoonjans, A. A. Sauve, J. Auwerx. The NAD^+ precursor nicotinamide riboside enhances oxidative metabolism and protects against high-fat diet induced obesity. Cell Metabolism, 2012, 15, 838-847. PMC3616313

H. Zhang, D. Ryu, Y. Wu, K. Gariani, X. Wang, P. Luan, D. D'Amico, E.R. Ropelle, M.P. Lutolf, R. Aebersold, K. Schoonjans, K.J. Menzies*, J. Auwerx*. (*co-corresponding authors) NAD^+ repletion improves mitochondrial and stem cell function and enhances lifespan in mice. Science, 2016, 352, 1436-43. PMID27127236

E. Katsyuba, A. Mottis, M. Zietak, F. DeFranco, V. vanderVelpen, K. Gariani, D. Ryu, L. Calabrini, O Matilainen, P. Liscio, N. Giacche, N. Stokar, D. Legouis, S. deSeigneux, J. Ivanisevic, N. Raffaelli, K. Schoonjans, R. Pelliciari. J. Auwerx. De novo NAD^+ synthesis enhances mitochondrial function and improves health. Nature, 2018, 563, 354-9. PMID30356218

(#5) We were amongst the first to establish in vertebrates the importance of **retrograde signaling pathways**—mitochondria→nucleus—as a mechanism to synchronize nuclear activity with mitochondrial function. Retrograde signaling should be considered an adaptive response, that is triggered by mitochondrial stress, such as seen upon activation of the mitochondrial unfolded protein response (UPR^{mt}), mitochondrial biogenesis, dynamics, and mitophagy. *First*, we showed that a proteostatic imbalance between mitochondrial proteins encoded in the nDNA and mtDNA—aka as mitonuclear protein imbalance—either through genetic (variation in expression of the mitochondrial ribosomal proteins) or pharmacological strategies (doxycycline) activates the UPR^{mt}. *Second*, we discovered that activation of mitochondrial biogenesis, by a variety of compounds such as rapamycin, resveratrol, as well as NAD^+ boosters, also induces a mitonuclear imbalance and a similar retrograde response. *Finally*, we demonstrated that mitophagy can also elicit a similar retrograde stress pathway. Of note, activating retrograde signaling—by mitochondrial biogenesis, mitonuclear proteostatic imbalance, and mitophagy—has not only beneficial effects on mitochondrial function, but also improved organismal health as demonstrated by its remarkable capacity to protect from amyloid beta disease (e.g. Alzheimer disease), enhance muscle function and increase lifespan. Together this ensemble of studies laid the cornerstones of the field of "*mitonuclear communication*" in vertebrates.

R. H. Houtkooper, L. Mouchiroud, D. Ryu, N. Moullan, E. Katsyuba, G. Knott, R.W. Williams, J. Auwerx. Mitonuclear protein inbalance as a conserved longevity mechanism. Nature, 2013, 497, 451-457. PMC3663447

L. Mouchiroud, R.H. Houtkooper, N. Moullan, E. Katsyuba, D. Ryu, C. Canto, A. Mottis, Y.-S. Jo, M. Viswanathan, K. Schoonjans, L. Guarente, J. Auwerx The NAD+/sirtuin pathway modulates longevity through activation of mitochondrial UPR and FOXO signaling. Cell, 2013, 154, 430-441. PMC3753670

D. Ryu, L. Mouchiroud, P. Andreux, E. Katsyuba, N. Moullan, A. Nicolet, E. Williams, P. Jha, G. Lo Sasso, D. Huzard, P. Aebischer, C. Sandi, C. Rinsch*, J. Auwerx* (*co-corresponding). Urolithin A induces mitophagy and prolongs lifespan in *C.elegans* and increases muscle function in rodents. Nature Med., 2016, 22, 879-88. PMID27400265

V. Sorrentino, M. Romani, L. Mouchiroud, J.S. Beck, H. Zhang, D. D'Amico, N. Moullan, F. Potenza, A.W. Schmid, S. Rietsch, S. E. Counts, J. Auwerx. Enhancing mitochondrial proteostasis reduced amyloid-beta proteotoxicity. Nature, 2017, 552, 187-193. PMID29211722

D. Additional Information: Research Support and/or Scholastic Performance

- **EPFL-ETH recurrent support** (Auwerx J); permanent; 3 calendar; Role: PI; CHF 1'000'000/yr; "Laboratory of integrative systems physiology"; basic and recurrent lab support
- **Global Research Laboratory (GRL) National Research Foundation of Korea** (Shong M); 9/01/2017-2/28/2023; 0.6 calendar; Role: Co-PI; KRW 843'000'000; "*The role of mitochondrial proteostasis in health and diseases*"; Analysis of cell-non-autonomous secreted factors (mitokines) released upon mitochondrial stress; No overlap
- **ERC-2017-AdG-LS2 787702** (Auwerx J); 11/1/2018-10/31/2023; 3.6 calendar; Role: PI; Euro 2'500'000 "*The mitochondrial unfolded Protein response*"*;* Characterization of the mitochondrial unfolded protein response in worms, cells, and mice; No Overlap
- **SNSF-31003A-179435** (Auwerx J); 2/1/2019-1/31/2023; 2.4 calendar; Role: PI; CHF 1'344'000 "*Genetic control of NAD^+ metabolism";* Characterization of NAD^+ metabolism in mouse populations and loss-of-function mouse models; No Overlap
- **Janssen Pharmaceuticals** (Auwerx J); 12/15/2018-12/15/2021; 2.4 calendar; Role: PI; CHF 3'300'000 "*Genetic determinants of Non-Alcoholic Steato-Hepatitis (NASH) and Chronic Kidney Disease (CKD)";* Characterization of genetic factors that control NASH and CKD in mouse populations; No Overlap