

20th Jan 2024

Re: Application for membership of the ISHR European Section Council

Dear Prof Davidson and Council members,

I hereby apply to join the Council of the ISHR European Section. Below, please find my reasons for applying and my qualifications for this role and in subsequent pages, a short CV.

I am an active cardiovascular researcher and have worked in this field for more than 20 years. Previously and related to this research, during my early career as a PhD student and first post-doc, I focussed on Ca²⁺ signalling in non excitable cells. More recently, my laboratory combined physiological studies with analysis of the role of the epigenome in cardiac remodelling during cardiomyocyte maturation, disease and ageing. Together with the use of single cell omics to dissect cell phenotype changes, this area has become a major part of my laboratory's efforts. Across different fields, I have published many highly cited articles and contributed authoritative reviews and commentaries. I consider that the broad range of my experience and the research themes in my lab equip me to contribute to the activities of the council of the ISHR-ES. Further, I have enjoyed participating, together with my PhD students and post-docs, in many cardiovascular meetings. Notably, in 2023, I was invited to present our work at the ISHR ES meeting in Porto, at the Excitation Contraction Coupling Gordon Conference, Epigenetic Mechanisms of Cardiovascular Disease Gordon Conference, The Physiological Society and the Australian Physiological Society meeting.

I am active in scientific societies and communities including the ISHR. I, and members of my lab have participated in ISHR meetings, which are an ideal 'home' for research in my lab, which focusses on basic mechanisms underlying cardiac function, remodelling and disease as its core. I am a member of the Scientific Program Committee for the ISHR Nara Congress 2025, I am a member of the Editorial Board of JMCC+ and have published reviews, commentaries, and research papers in JMCC and JMCC+. Notable additional service to the community include - secretary and nucleus member of the Working Group on Cellular Electrophysiology and president of the Working Group on Basic Research of the Belgian Society of Cardiology.

Important to contributing as a member of the ISHR ES Council, I have an enthusiasm for scientific research, to understand cellular mechanisms underlying alterations in myocardial function and to employ innovative and contemporary techniques and animal models to test hypotheses. Further, I consider it important to have an eye to translation. In this regard, I use samples from human patients in my research, use large animal preclinical models of disease and test small molecule and genetic approaches to ameliorate disease pathologies in animal models and human myocytes. My interest in this area has developed through my lab move in 2014 to join the Laboratory of Experimental Cardiology with Prof K Sipido in KULeuven where large mammal models of disease, advanced imaging technologies and availability of tissue through the cardiac transplant programme enable progress. Collaboration with clinicians at our centre further adds to capacity.

I see that a key role of a Council member of the ISHR ES is to provide an environment/community and support for the development of the careers and experience of its PhD student and post-doc members.



Through providing a friendly and open platform for discussion of their research and mentoring, career progression and scientific development of the next generation of scientists can be improved. As part of this, I would support devoting meeting sessions to early career investigators and/or, as in the case of GRC, an ECI 1-day symposium prior to the ISHR main meeting. None of these aims would be possible without interesting meetings at the cutting edge of CV research. Having a strong council with diverse perspectives who work to ensure equal opportunities for all in a transparent manner is essential to achieve this goal.

Building networks is vital to all our progress and to extending our research capacity and ideas. I have enjoyed work as a scientist in the UK (PhD student, post-doc and PI), the US (Post-doc) and now in Belgium (Prof). In these locations, I have mentored post-docs and students who have gone on to successful careers in both academia and other science-related professions. I would hope that I can bring this experience and different perspectives to my role as a Council member. Through working in these different environments, and by being actively involved in collaborative grants, I have built up a range of networks within and outside of Belgium/UK, which I would wish to represent on the Council.

I hope the information I have provided demonstrates my motivation to join the Council of the European Section of the ISHR and to participate in achieving its mission.

Yours sincerely,

H. Llewelyn Roderick

Personal Information:

Hywel Llewelyn Roderick, B.Sc., Ph.D. Professor (Hoogleraar) and head of the Laboratory of Experimental Cardiology, Department of Cardiovascular Sciences, KULeuven.

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Professional career:

- 2016-** Affiliated Investigator, K.G. Jebsen Center for Cardiac Research, University of Oslo, Oslo, Norway.
- 2014-** Professor (BOF-ZAP), Laboratory of Experimental Cardiology, Department of Cardiovascular Sciences, KULeuven
- 2014-** Affiliated Lecturer, University of Cambridge.
- 2010-2014** Group leader with Tenure, Babraham Institute, Cambridge, UK.
- 2005-2012** Royal Society University Research Fellow, Department of Pharmacology, University of Cambridge, Cambridge, UK
- 2004-2010** Group Leader (Tenure track), Babraham Institute, Cambridge, UK.
- 2001-2004** Postdoctoral Research, M. D. Bootman and Sir M. J. Berridge FRS, Babraham Institute, Cambridge, UK.
- 1997-2001** Postdoctoral Research, P. Camacho, Dept. Physiology, University of Texas Health Science Center, San Antonio, Texas.

Education:

- 1993-97** Ph.D. Dept. Medical Biochemistry, University of Wales College of Medicine, Cardiff, UK.
- 1989-92** B.Sc., Zoology and Genetics. Dept. Pure and Applied Biology, UWCC, Cardiff, UK.

Research Themes:

Signalling and the epigenome in the control of cardiac myocyte fate during health, disease and ageing. This research is divided between:

1. *Defining the contribution of the epigenome to determining the differentiated state of adult cardiac myocytes and in the remodeling of the heart in response to physiological and pathological stressors including during normal ageing.* Through these analysis we aim to identify strategies that can be employed to reverse the deleterious functional remodelling associated with disease and ageing. These strategies will target reactivation of cell cycle activity to improve regeneration of damaged tissue and suppression of disease associated gene transcription programmes. To these ends we employ next generation sequencing including single cell sequencing, genome wide epigenomic analysis, genetic and surgical models of cardiac disease, and human tissue.
2. *Delineating contribution of Ca²⁺ signalling to disease associated structural, functional and physiological remodelling of cardiac myocytes.* A particular interest is in the dual roles of Ca²⁺ signaling microdomains regulated by IP₃ in disease and ageing-associated remodelling of excitation contraction coupling and activation of hypertrophic gene transcription. Specifically how specificity is encoded by a given Ca²⁺ signal. To these ends we perform combined cellular electrophysiology and Ca²⁺ imaging approaches, employ genetically encoded Ca²⁺ indicators, tissue preparations, large (pig, sheep) and small mammal models of disease, human cell/tissue analysis and super resolution imaging.

Publications (h index 51, >19300 citations):

1. Dries, E., G. Gilbert, **H.L. Roderick** & K.R. Sipido. (2023) The ryanodine receptor microdomain in cardiomyocytes. *Cell Calcium* 114, 102769.

2. Jin, X., A. Meletiou, J. Chung, A. Tilunaite, K. Demydenko, E. Dries, R.D. Puertas, M. Amoni, A. Tomar, G. Gilbert, P. Claus, C. Soeller, V. Rajagopal, K. Sipido, and **H.L. Roderick**. 2023. InsP3R-RyR channel crosstalk augments sarcoplasmic reticulum Ca²⁺ release and arrhythmogenic activity in post-MI pig cardiomyocytes. *J Mol Cell Cardiol.* 179:47–59. doi:10.1016/j.yjmcc.2023.03.015.
3. Amoni, M., D. Vermoortele, S. Ekhteraei-Tousi, R.D. Puertas, G. Gilbert, M. Youness, B. Thienpont, R. Willems, **H.L. Roderick***, P. Claus*, and K.R. Sipido*. (2023). Heterogeneity of Repolarization and Cell-Cell Variability of Cardiomyocyte Remodeling Within the Myocardial Infarction Border Zone Contribute to Arrhythmia Susceptibility. *Circulation Arrhythmia Electrophysiol.* 16:e011677. doi:10.1161/circep.122.011677.* co Senior Author.
4. Leybaert, L., M.A.J.D. Smet, A. Lissoni, R. Allewaert, **H.L. Roderick**, G. Bultynck, M. Delmar, K.R. Sipido, and K. Witschas. (2023). Connexin hemichannels as candidate targets for cardioprotective and anti-arrhythmic treatments. *J Clin Investigation.* 133:e168117. doi:10.1172/jci168117.
5. Tomar, A., S. Ekhteraei-Tousi and **H.L. Roderick**. (2023). DEG (differentially expressed gene) or not DEG that is the question: Should we compare between datasets or not? *J Mol Cell Cardiol Plus.* 3:100029. doi.org/10.1016/j.jmccpl.2022.100029.
6. Chung, J., A. Tilūnaitė, D. Ladd, H. Hunt, C. Soeller, E.J. Crampin, S.T. Johnston, **H.L. Roderick***, and V. Rajagopal*. (2023). IP3R activity increases propensity of RyR-mediated sparks by elevating dyadic [Ca²⁺]. *Math Biosci.* 355:108923. doi:10.1016/j.mbs.2022.108923. Co-senior author.
7. Jin, X., M. Amoni, G. Gilbert, E. Dries, R.D. Puertas, A. Tomar, C.K. Nagaraju, A. Pradhan, D.I. Yule, T. Martens, R. Menten, P.V. Berghe, F. Rega, K. Sipido, and **H.L. Roderick**. (2022). InsP3R–RyR Ca²⁺ channel crosstalk facilitates arrhythmias in the failing human ventricle. *Basic Res Cardiol.* 117:60. doi:10.1007/s00395-022-00967-y.
8. Demydenko, K., S. Ekhteraei-Tousi, and **H.L. Roderick**. (2022). Inositol 1,4,5-trisphosphate receptors in cardiomyocyte physiology and disease. *Philosophical Transactions Royal Soc B.* 377:20210319. doi:10.1098/rstb.2021.0319.
9. Robinson, E.L., F.M. Drawnel, S. Mehdi, C.R. Archer, W. Liu, H. Okkenhaug, K. Alkass, J.M. Aronsen, C.K. Nagaraju, I. Sjaastad, K.R. Sipido, O. Bergmann, J.S.C. Arthur, X. Wang, and **H.L. Roderick**. 2022. MSK-Mediated Phosphorylation of Histone H3 Ser28 Couples MAPK Signalling with Early Gene Induction and Cardiac Hypertrophy. *Cells.* 11:604. doi:10.3390/cells11040604
10. Amoni, M., P. Claus, E. Dries, C. Nagaraju, S.D. Buck, B. Vandenberk, S. Ingelaere, D. Vermoortele, **H.L. Roderick**, K. Sipido, and R. Willems. 2021. Discrete sites of frequent premature ventricular complexes cluster within the infarct border zone and coincide with high frequency of delayed afterdepolarizations under adrenergic stimulation. *Heart Rhythm* 18:1976-1987. doi:10.1016/j.hrthm.2021.07.067.
11. Demydenko, K., K.R. Sipido, and **H.L. Roderick**. 2021. Ca²⁺ release via InsP3Rs enhances RyR recruitment during Ca²⁺ transients by increasing dyadic [Ca²⁺] in cardiomyocytes. *J Cell Sci.* 134: doi:10.1242/jcs.258671.
12. Puertas, R.D., R. Arora, S. Rome, B. Asatryan, **H.L. Roderick**, and P. Chevalier. 2021. Epigenetics in atrial fibrillation: a reappraisal. *Heart Rhythm.* doi:10.1016/j.hrthm.2021.01.007.
13. Inhibition of aquaporin-1 prevents myocardial remodeling by blocking the transmembrane transport of hydrogen peroxide. 2020. Montiel, V., R. Bella, L.Y.M. Michel, H. Esfahani, D.D. Mulder, E.L. Robinson, J.-P. Deglasse, M. Tiburcy, P.H. Chow, J.-C. Jonas, P. Gilon, B. Steinhorn, T. Michel, C. Beauloye, L. Bertrand, C. Farah, F.D. Zotti, H. Debaix, C. Bouzin, D. Brusa, S. Horman, J.-L. Vanoverschelde, O. Bergmann, D. Gilis, M. Rooman, A. Ghigo, S. Geninatti-Crich, A. Yool, W.H. Zimmermann, **H.L. Roderick**, O. Devuyst, and J.-L. Balligand. *Sci Transl Med.* 12:eaay2176. doi:10.1126/scitranslmed.aay2176.
14. Robinson EL, Alkass K, Bergmann O, Maguire JJ, **Roderick HL***, Davenport AP. 2020. Genes encoding ACE2, TMPRSS2 and related proteins mediating SARS-CoV-2 viral entry are upregulated with age in human cardiomyocytes. *J Mol Cell Cardiol.* 147:88-91. doi: 10.1016/j.yjmcc.2020.08.009. Shared senior author.

15. Gilbert, G., K. Demydenko, E. Dries, R.D. Puertas, X. Jin, K. Sipido, and **H.L. Roderick**. 2019. Calcium Signaling in Cardiomyocyte Function. *Cold Spring Harb Perspect Biol* doi:10.1101/cshperspect.a035428
16. Nagaraju, C.K., E.L. Robinson, M. Abdeselem, S. Trenson, E. Dries, G. Gilbert, S. Janssens, J. Van Cleemput, F. Rega, B. Meyns, **H.L. Roderick**, R.B. Driesen, and K.R. Sipido. 2019. Myofibroblast Phenotype and Reversibility of Fibrosis in Patients With End-Stage Heart Failure. *J Am Coll Cardiol*. 73:2267–2282. doi:10.1016/j.jacc.2019.02.049.
17. Smyrniak, I., N. Goodwin, D. Wachten, J. Skogestad, J.M. Aronsen, E.L. Robinson, K. Demydenko, A. Segonds-Pichon, D. Oxley, S. Sadayappan, K. Sipido, M.D. Bootman, and **H.L. Roderick**. 2018. Contractile responses to endothelin-1 are regulated by PKC phosphorylation of cardiac myosin binding protein-C in rat ventricular myocytes. *J Mol Cell Cardiol*. 117:1–18. doi:10.1016/j.yjmcc.2018.02.012.
18. Archer, C.R., E.L. Robinson, F.M. Drawnel, and **H.L. Roderick**. 2017. Endothelin-1 promotes hypertrophic remodelling of cardiac myocytes by activating sustained signalling and transcription downstream of endothelin type A receptors. *Cell Signal*. 36:240–254.
19. Thienpont, B., J.M. Aronsen, E.L. Robinson, H. Okkenhaug, E. Loche, A. Ferrini, P. Brien, K. Alkass, A. Tomasso, A. Agrawal, O. Bergmann, I. Sjaastad, W. Reik, and **H.L. Roderick**. 2017. The H3K9 dimethyltransferases EHMT1/2 protect against pathological cardiac hypertrophy. *J Clin Invest*. 127:335–348. doi:10.1172/JCI88353.
20. Drawnel, F.M., Wachten, D., Molkentin, J.D., Maillet, M., Aronsen, J.M., Swift F, Sjaastad, I., Liu, N., Catalucci, D., Mikoshiba, K., Hisatsune, C., Okkenhaug, H., Andrews, S.R., Bootman, M.D., **Roderick, H.L.** (2012) Mutual antagonism between IP3R2 and miRNA-133a regulates calcium signals and cardiac hypertrophy. *J Cell Biol*. 199:783–798. Editorial Highlight 'In this Issue' and Cover Image.
21. Bootman, M.D., Smyrniak, I., Thul, R., Coombes, S., and **Roderick, H.L.** (2011). Atrial cardiomyocyte calcium signalling. *Biochim Biophys Acta*, **1813**, 922-934.
22. Fearnley, C.J., **Roderick, H.L.*** and Bootman, M.D. (2011) Calcium Signaling in Cardiac Myocytes. *Cold Spring Harb Perspect Biol*. 2011 Aug 29. pii: cshperspect.a004242v1. doi: 10.1101/cshperspect.a004242. Review. *Equal contribution.
23. Smyrniak, I., Mair, W., Harzheim, D., Walker, S.A., **Roderick, H.L.*** and Bootman, M.D. (2010) Comparison of the T-tubule system in adult rat ventricular and atrial myocytes, and its role in excitation-contraction coupling and inotropic stimulation. *Cell Calcium*, **47**, 210-223. Co-corresponding author.
24. Harzheim, D., Movassagh, M., Foo, R.S., Ritter, O., Tashfeen, A., Conway, S.J., Bootman, M.D. and **Roderick, H.L.** (2009) Increased InsP3Rs in the junctional sarcoplasmic reticulum augment Ca²⁺ transients and arrhythmias associated with cardiac hypertrophy. *Proc Natl Acad Sci U S A*, **106**, 11406-11411. (Highlighted in Physiology)
25. Higazi, D.R., Fearnley, C.J., Drawnel, F.M., Talasila, A., Corps, E.M., Ritter, O., McDonald, F., Mikoshiba, K., Bootman, M.D. and **Roderick, H.L.** (2009) Endothelin-1-stimulated InsP3-induced Ca²⁺ release is a nexus for hypertrophic signaling in cardiac myocytes. *Mol Cell*, **33**, 472-482. Editor's Choice Science Signalling.
26. **Roderick, H.L.** and Cook, S.J. (2008) Ca²⁺ signalling checkpoints in cancer: remodelling Ca²⁺ for cancer cell proliferation and survival. *Nat Rev Cancer*, **8**, 361-375.
27. Bootman, M.D., Harzheim, D., Smyrniak, I., Conway, S.J. and **Roderick, H.L.** (2007) Temporal changes in atrial EC-coupling during prolonged stimulation with endothelin-1. *Cell Calcium*, **42**, 489-501.
28. Proven, A., **Roderick, H.L.***, Conway, S.J., Berridge, M.J., Horton, J.K., Capper, S.J. and Bootman, M.D. (2006) Inositol 1,4,5-trisphosphate supports the arrhythmogenic action of endothelin-1 on ventricular cardiac myocytes. *J Cell Sci*, **119**, 3363-3375. (Communicating Author)

29. Kasri, N.N., Holmes, A.M., Bultynck, G., Parys, J.B., Bootman, M.D., Rietdorf, K., Missiaen, L., McDonald, F., De Smedt, H., Conway, S.J., Holmes, A.B., Berridge, M.J. and **Roderick, H.L.** (2004) Regulation of InsP3 receptor activity by neuronal Ca²⁺-binding proteins. *Embo J*, **23**, 312-321.
30. Berridge, M.J., Bootman, M.D. and **Roderick, H.L.** (2003) Calcium signalling: dynamics, homeostasis and remodelling. *Nat Rev Mol Cell Biol*, **4**, 517-529.

Current Research Funding:

FWO Project Grant (01/01/2023-31/12/2026; G063023N): HLR PI KUL with Leybaert UGhent PI, and co-PIs Sipido (KUL) and Labro (UGhent). Connexin-43 hemichannels and pro-arrhythmic mediators in cardiac hypertrophy and heart failure.

FWO Postdoctoral Researcher (Junior) to Onne Ronda (01/10/2022-30/09/2025; 3M220375) (Sponsor): Investigating the role of DNA methylation in the failing and in the ageing heart.

KULeuven Internal funds (01/10/2021-30/09/25; C1 grant #C14/21/093). HLR PI/coordinator, co-PIs Rega, Martinood, Sipido. Understanding the Vulnerability of the Ageing Heart.

FWO Project Grant (01/01/2021-31/12/2023; G097021N): HLR co-PI with Karin Sipido PI, and co-PIs Piet Claus, Rik Willems and Eef Dries. Linking functional microarchitecture of the myocardial infarction borderzone to arrhythmogenesis.

iBOF grant (01/01/2021-31/12/2025; 20-VLIR-iBOF-027) with Hein Heidbuchel Antwerp and Nele Vandersickel Ghent. Defining atrial myopathy in aging and disease DIAMOND Consortium.

KU Leuven Global PhD Partnerships with Melbourne University (2020-2025) (KU LEUVEN INTERNAL FUNDS Reference nr.: GPUM/21/036). HLR KUL PI and V Rajagopal UM PI) Subcellular Ca²⁺ signalling microdomains regulating cardiomyocyte growth and function. 2 x PhD studentships.

FWO Project Grant (G0C6419N (internal Ref: ZKD5718); 01/01/2019 31/12/2023): Methylation of histone H3 lysine 9 by the Euchromatic Histone Methyl Transferases (EHMT1/2) regulates cardiac myocyte growth and proliferative responses.

KG Jebsen Center for Cardiac Research (KGJ-CCR), Oslo, Norway of which I am an Affiliated Investigator).

Teaching:

- Actively involved in teaching cardiovascular sciences and epigenetics to the Biomedical Sciences and medical students at KULeuven and to Pharmacology/medical students at my previous affiliation at the Dept Pharmacology, University of Cambridge.
- Promoter of 5 and co-promoter of 5 PhD student.
- 33 PhD students supervised/co-supervised including 10 in progress
- Thesis advisory committee of 36 students.
- Examiner of 23 PhDs.

Congress participation:

- ISHR 2025, NARA. Symposium committee member.
- Invited speaker at 41 National and International conferences including ISHR-ES 2023, 5 Gordon conferences, 1 FASEB Summer conference, ESC Congress, FCVB, Heart Rhythm Society (USA), HFA Winter meeting and European Calcium Society.
- Contributed to organisation and chaired sessions at Life Sciences 2007 (combined UK societies) FCVB, Europhysiology, Belgian Society of Cardiology.
- SessionChair/discussion leader at Gordon Research Conferences on Cardiovascular Epigenetics and on Calcium Signalling, Calcium Signalling Gordon Keynan Research Symposium, Life Sciences 2007, FCVB 2024.
- Oral presentations Gordon Conferences x 3, The Physiological Society.
- 31 Departmental Seminars

Society memberships:

- President of the Belgian Working Group of Basic Research in Cardiology (BWG-BRC) of the Belgian Society of Cardiology
- Secretary and nucleus member of the ESC Working Group on Cardiac Electrophysiology
- Member of the ESC.
- Member of the ISHR.
- The Physiological Society
- European Calcium Society.

Reviewing:

- 2023- Editorial Board Member JMCC+
- Editorial board member of Cardiovascular Research, Frontiers in Oncology and Clinical Epigenetics.
- Ad hoc Referee for Circulation Research, Cell, Nature, Circulation, PNAS and other top line journals.
- Referee for National/International Research funding organisations: ERC, MRC, BBSRC, Wellcome and BHF in the UK, FWO (Belgium), CNRS (France), NWO (Netherlands) and Telethon (Italy).

Awards:

- Odysseus Award from the FWO, Belgium (2014-2019)
- Royal Society University Research Fellowship, The Royal Society, UK (2004-2012)