

From Africa with love: A Festschrift for Robert P. Millar

Robert (Bob) Millar will retire in 2024, after a long and distinguished career in neuroendocrinology. Claire and I have been working with Bob for some years and took on the task of organising a Festschrift to celebrate his contributions to the community and his 80th birthday, which was held in South Africa at the beginning of February 2024. Bob's accomplishments in biomedical research during a period of over 60 years are exceptional, both in the fundamental discoveries he has made and also in his ability to translate them into clinical practice for the therapy of reproductive health and hormone-dependent diseases.

Having grown up in the bush in Zimbabwe, Bob is irrevocably tied to the wildlife of Africa, and we decided to hold the Festschrift in Kruger National Park. Kruger is greater in size than Belgium, and its extraordinary heritage was brokered by Paul Kruger, a prominent Boer leader and antagonist of colonial Britain. Kruger National Park harbours the last remnants of the megamammals that dominated the planet during the Pleistocene. These huge mammals once roamed throughout northern Europe, Asia, and North America, where they eventually became extinct. Africa is their last refuge and, in Kruger National Park, you can see the world in pristine condition, as it used to be aeons ago. It is a magical place, and having once been there, you cannot avoid falling in love with Africa. Douglas Adams, the author of the "Hitchhiker's Guide to the Galaxy", sought out the planet's endangered species and some years later wrote his book "Last Chance to See". We all hope that this was not our last chance to see many of these magnificent creatures.

Bob was born in South Africa and grew up in Zimbabwe, where he received his BSc (Hons), followed by an MSc (London) and PhD (Liverpool) in the UK, before taking up positions at the University of Cape Town and then the University of Edinburgh. He returned to South Africa in 2011 and, prior to his retirement, was Director of the Centre for Neuroendocrinology at the University of Pretoria, a Senior Research Fellow in the Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, a Research Fellow at the Centre for Discovery Brain Sciences, University of Edinburgh, and an Emeritus Professor at the University of St Andrews.

Bob's research has focused on the neuroendocrine regulation of reproduction. He was the first to establish that the brain hormone gonadotropin-releasing hormone (GnRH) is produced from a precursor polypeptide and to identify the structures of novel GnRHs. A significant landmark was his achievement in isolating a novel GnRH from 600,000 chicken brains. His group was also involved in the first cloning of the GnRH receptor and subsequent discovery and cloning of the GnRH type II receptor subtype. Together with collaborators, his research groups have made major contributions in delineating GnRH binding sites and the molecular mechanisms underlying receptor activation and coupling to signalling pathways, which has led to the development of GnRH analogue therapeutics for the treatment of a wide range of hormone-dependent diseases. His groups' research on the distinct antiproliferative effects of GnRH analogues on tumour cells has revealed novel roles for GnRH signalling and highlighted the concept of ligand-induced-selective-signalling (biased signalling) by GnRH analogues, which have implications for new GnRH therapeutics.

Most recently Bob has applied his expertise in G protein-coupled receptor (GPCR) function to understanding the mechanisms of action of novel GPCRs involved in reproduction, including the receptors for kisspeptin, neurokinin B (NKB) and gonadotropin-inhibitory-hormone. He has made a major contribution in developing kisspeptin antagonists, which are now

extensively used in research in dissecting metabolic and hormonal neuroendocrine regulation of reproductive hormones, and as potential therapeutics in hormone-dependent diseases. His research has been characterised by the continuation of basic studies through to clinical applications, and he has been involved in introducing ten neuropeptides and analogues into the treatment of humans. Some of these are now used in clinics for treatments of diseases such as prostatic cancer, endometriosis, infertility, and polycystic ovarian syndrome. One example is his involvement in the development of NK1 antagonists that are now in clinics and exploring their application in treating hot flushes and polycystic ovarian syndrome.

He has contributed to demonstrating that inactivating mutations in human GPCRs can be rescued by cell-permeant small molecules that bind and stabilise the receptor (pharmacological chaperones), which has huge potential for the treatment of patients with diverse diseases and is more feasible than gene editing. A focus of his research group has been on the rescue of inactivating mutations in the human GnRH, luteinising hormone, follicle-stimulating hormone and neurokinin 3 receptors. Having established proof of concept, the group is now initiating studies to restore function to LH receptor mutants in mice harbouring these mutations and in patients.

Bob can be described as a proper zoologist, having worked not only on mice, rats, and humans but also on invertebrates, fish, amphibians, reptiles, birds, and several wild mammal species, including rock hyrax, springhaas, mole rats, musk shrew, long-fingered bats, antelopes, lions, spotted hyenas, Ethiopian wolves, African wild dogs, rhinoceros, pygmy hippopotamus and marmoset and rhesus monkeys.

Bob has published some 500 papers in peer-reviewed journals and 18 patents, and his achievements have been recognised by many awards, including the Wellcome gold medal, the Oppenheimer gold medal, the Geoffrey Harris Laureate of the International Neuroendocrine Federation, the Ernst and Berta Scharrer Laureate of the International Society of Comparative Endocrinology, the John F Herschell gold medal, the Harry Oppenheimer Fellowship, and the platinum medal of the South African Medical Research Council for lifetime achievements in medical research. He received the lifetime achievement award of the Society for Endocrinology and Diabetes of South Africa and the African Union Kwame Nkrumah Continental award for scientific excellence. In 2021 he was awarded the laureate of the World Academy of Sciences.

Bob is a Fellow of the Royal Society of Edinburgh, a Fellow of the Royal Society of South Africa, and a member of the Academy of Science of South Africa. He has held the position of president/chairman of several societies and was elected President of the International Neuroendocrinology Federation 2016-2020. He has served on the board of many international journals and was Editor-in-Chief of Neuroendocrinology 2005-2020 and is currently Editor-in-Chief of the Translational and Clinical Neuroendocrinology strand of the Journal of Neuroendocrinology.

Working with Bob can be challenging at times due to his strong-natured personality, but he is respected for his determined attitude and his refusal to take 'no' as an answer. He is an inspiring research leader, colleague and friend. We wish Bob a happy retirement now that he has decided to spend more time with his wife Wendy at Mana (his property in Kruger). Those having the privilege to stay there and simply sit on a bench next to the river will find their love for Africa. There is nothing more exhilarating than being challenged by elephants on the way to Mana or woken up by the roaring of lions just outside your bedroom window. If you ever get the chance to stay with the Millars, make sure that Wendy is around – when one of us (Mike) stayed alone with Bob for several weeks, we had braai (South African BBQ) for dinner every night. There were four options: chicken or beef, still raw or burned.

Bob is looking forward to continuing some of his research and scholarly activities in his emeritus status, and he will continue to write, to be active in editorial matters and to support his close collaborators. We hope to undertake another lion or spotted hyena study with him in the very near future.

This issue contains contributions from the invited speakers at the Festschrift, comprising a range of friends, colleagues, former students and collaborators from Bob's illustrious career, who have written short articles on their fields of biomedical research, and we hope that these articles will be a 'roaring' success and make an excellent special issue of the Journal.

Mike Ludwig and Claire Newton