Name	ROBIN LOVELL-BADGE
Position	Senior Group Leader Ambassador for Public Engagement
Year joined *(Crick or founder institute)*	1988

Career History

1975-1977: PhD in Embryology, University College, London
1978-1981: Postdoctoral Research Associate, Department of Genetics, University of Cambridge
1981-1982: EMBO Long Term Fellowship, Institute Jacques Monod, Paris
1982-1988: MRC Staff Position, MRC Mammalian Development Unit, University College, London

Major Awards, Honours and Prizes

1993: Elected, Member of EMBO
1995: Louis Jeantet Prize for Medicine
1996: The Amory Prize (awarded by the American Academy of Arts and Sciences)
1999: Elected, Fellow of the Academy of Medical Sciences
2001: Elected, Fellow of the Royal Society
2002: Elected, Fellow of the Royal Society of Arts
2008: The Feldberg Foundation Prize
2010: The Waddington Medal of the British Society for Developmental Biology
2011: Elected, Fellow of the Royal Society of Biology
2018: CBE awarded for services to science and public engagement.
2018: Elected, Fellow of the American Association for the Advancement of Science
2018: The Galton Lecture 2018, and honorary life fellowship of the Galton Institute

1996-present, Visiting Professor, Faculty of Medical Sciences, University of Hong Kong, Hong Kong
2006-present, President of the Institute of Animal Technology
2009-2015: Distinguished Visiting Professor, University of Hong Kong, Hong Kong
2013-present, Honorary Professor, Division of Biosciences, Faculty of Life Sciences, University College, London
2015-present, Special Visiting Professor, University of Hong Kong, Hong Kong
2016-present, Visiting Professor, Division of Craniofacial Development & Stem Cell Biology, Dental Institute, King's College London

Membership of external committees, editorial boards, review panels, SABs etc

- 2005-present, member of the Steering Committee of the Hinxton Group
- 2006–2017, Science Media Centre, Advisory Board
- 2006-present, Human Fertility and Embryo Authority (HFEA); Co-opted member of the Scientific and Clinical Advances Advisory Committee
- 2007-present, Editorial Board: 'Sexual Development'
- 2009-present, BBVA Foundation, Frontiers of Knowledge Awards. Member of the Jury for the Biomedicine Award
- 2010-present, Editorial Board: 'Biology of Sex Differences'

- 2011-2017, Co-chair/member of HFEA Panel providing a “Review of scientific methods to avoid mitochondrial disease”
- 2011–2017, UAR, Member of Council
- 2011-2019, Feldberg Foundation Award Committee; Member and chair (2018-19)
- 2012-present, Public Library of Science (PLOS); Board Member
- 2013-present, Member of the Public Engagement Committee of the Royal Society
- 2014-present, Sense About Science; Member of Board of Trustees
- 2015-present, Member of ISSCR Public Policy Committee
- 2015-present, US National Academies of Sciences and Royal Society “Human Genome-Editing Initiative: (i) Member of the Presidents’ Advisory Group. (ii) Member of the organizing committee for the International Summit Meeting, Washington DC, USA, 1-3 December 2015. (iii) Member of the Study Committee that produced a Report: “Human Genome Editing: Science, Ethics and Governance” (published 14 February 2017). (iv) Member of the organizing committee for the Second International Summit on Human Genome Editing, Hong Kong, 27-29 November 2018. (v) Chair of the organizing committee for the Third International Summit on Human Genome Editing, to be held in London, 2021.
- 2016-present, Member of External Scientific Advisory Board, Institute of Child Health GOS, UCL
- 2016-2018, Royal Society; Member of Nominations Committee
- 2017-2018: Member of IAP Committee: “Assessing the Security Implications of Genome Editing Technology”.
- 2017-present, Royal Society; Chair of “Genetic Technologies Programme”
- 2019-present, Progress Educational Trust; Chair of the Board of Trustees
- 2019-present, Member of the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing.
- 2019-2021, Chair of ISSCR Guidelines Working Group

Lab Name	***Stem Cell Biology and Developmental Genetics Laboratory***

Research programme and achievements

The main goal of the lab is to understand mechanisms underlying cell fate decisions, choosing a number of tractable and clinically relevant systems in the embryo and the adult, including stem cell populations. Many of these involve *Sox* genes, which encode transcription factors that often act as pioneers, and understanding these is also a common theme in our work. Sex determination and differentiation have been a main focus for many years, but CNS and pituitary development, and the biology and role of stem cells in these systems have also been major topics of our research and continue to be so. The work is of clinical relevance, both because it can help reveal the cause of disorders or syndromes, but also because the ability to manipulate cell fate choices is important for regenerative medicine.

Since 2015, our main achievements are:
• Determined novel genetic causes and provided understanding of the mechanisms underlying several cases of human Disorders of Sex Differentiation (DSDs). This has been achieved through our work in the mouse, often with our clinical collaborators
• Characterised the regulation of *Sox9* during sex determination, identifying a critical early acting enhancer (amongst a very long and complex regulatory region) that acts at the pivotal point of the decision to become a Sertoli rather than granulosa cell

• Shown the critical role for *Foxl2* and *Dmrt1* in sex determination in the chick. This is a collaboration with the Roslin Institute and has involved the development of novel methods permitting efficient genome editing and germline transmission in the chick
• Discovered mechanisms that could be responsible for the 4:1 male:female sex bias seen in Hirschsprung's Disease. This has involved studying mouse models of Hirschsprung's where we have found an unexpected sex bias in survival at birth, and studies on enteric nervous system development in male and female mice, showing precocious development in the latter
• Through studying the role in the developing CNS of Sox9, which is required for glial cell differentiation, we have identified an astrocytic scaffold required for migration of neuronal progenitors into the dentate gyrus and for normal hippocampus development and function. This work also reveals differences in the gene regulatory network involved in glial cell specification between the brain and spinal cord
• Characterised the role of several *Sox* genes and their targets (including Notch) in cell fate decisions within the CNS and pituitary
• Expanded on previous findings showing that the cell cycle inhibitor p27Kip1 can also act as a transcriptional repressor of Sox2, connecting proliferative state and Sox2 function, and understanding how this leads to the development of intermediate lobe tumours in p27 null animals

We are continuing our work on early events in sex determination, in the mouse and chick, but we are also exploring how gonadal sex is maintained. Deletion of *Foxl2* in the adult leads to gonadal sex reversal from ovaries to testis-like organs and understanding this at a molecular and cellular level will be relevant to regenerative medicine. We will also continue to explore *Sox* gene function in the developing and adult CNS, but we have also begun to use them as tools to explore sex differences in the CNS and in neural stem cell populations. We are also continuing work on pituitary stem cells *in vivo*, characterising how these respond to physiological changes, and on how systemic and external factors can influence the hypothalamus and its control of pituitary function. All of these programmes of work are rooted in generating fundamental insights into how decisions of cell fate are established and maintained, but they also have relevance to clinical situations.

Research outputs

Cheung, L., Le Tissier, P., Treier, M., Lovell-Badge, R. and Rizzoti, K. (2018). *NOTCH activity differentially affects alternative cell fate acquisition and maintenance*. eLife 7:e33318. DOI: 10.7554/eLife.33318
Notch signalling tends to maintain an undifferentiated state in progenitor cells, but here we showed that in the embryonic pituitary, while this is the case in one distinct lineage, (POMC cells, where activation can induce a regression towards a progenitor-like state), Notch signalling has no effect on cell fate specification in the POU1F1 lineage. These results have implications for pituitary development, plasticity and regeneration.

Gonen, N., Futtner, C.R., Wood, S., Garcia-Moreno, S.A., Salamone, I.M., Samson, S.C., Sekido, R., Poulat, F., Maatouk, D.M, and Lovell-Badge, R. (2018). *Sex reversal following deletion of a single distal enhancer of Sox9*. Science 360, 1469-1473. DOI: 10.1126/science.aas9408
This systematic study revealed the complexity of the *Sox9* regulatory region, but just one enhancer, "Enh13", was shown by mutation studies to be essential for testis and subsequent male development. *Sox9* expression is at the same very low level in XY Enh13 mutant embryos as in control XX gonads. Enh13 is efficiently bound by Sry *in vivo* and functions to initiate Sertoli cell fate during a short time window. This is in contrast to

other redundant enhancers (e.g. TES) that bind Sry, but act later. This study helped explain Disorders of Sex Differentiation (DSDs), due to deletions and duplications mapping far upstream of Sox9, where the human Enh13 equivalent is located, as well as showing that some enhancers can be pioneering rather than redundant.

Guioli, S., Zhao, D., Nandi, S., Clinton, M. and Lovell-Badge, R. (2020) *In the chick embryo, estrogen can induce chromosomally male ZZ left gonad epithelial cells to form an ovarian cortex, which supports oogenesis*. Development 147, 4. DOI: 10.1242/dev.181693
In the chick, many sex-specific characteristics are due to cell autonomous activity of the sex chromosomes, rather than as a response to gonadal hormones. However, we showed here that an ovarian cortex can form independently of the phenotypic sex of the medulla as long as oestrogen, acting via ERalpha, is provided. The presence of a medulla with an "intersex" or male phenotype may compromise germ cell progression into meiosis, causing cortical germ cells to remain in an immature state in the embryo. This may be relevant to human biology, where teratomas develop when germ cells are in an inappropriate environment.

Eozenou, C.*, Gonen, N.*, Touzon, M.S.*, Jorgensen. A., Yatsenko, S.A., Fusee, L., Kamel, A., Gellen, B., Guercio, G., Singh, P., Witchel, S., Berman, A.J., Mainpal, R., Totonchi, M., Mohseni Meybodi, A., Askari, M., Merel, T., Bignon-Topalovic, J., Migale, R., Costanzo, M., Marino, R., Ramirez, P., Perez Garrido, N., Berensztein, E., Mekkawy, M.K., Schimenti, J.C., Bertalan, R., Mazen, I., McElreavey, K.*, Belgorosky, A.*, Lovell-Badge, R.*, Rajkovic, A.*, Bashamboo, A.* (2020) *Testis formation in XX individuals resulting from novel pathogenic variants in Wilms' tumor 1 (WT1) gene*. Proc. Natl. Acad. Sci. USA. 117, 13680-13699. DOI: 10.1073/pnas.1921676117
Through analysis of a large collection of clinical cases of Disorders of Sex Differentiation (DSDs), and a mouse model, we showed that unlike previous association of WT1 variants with XY female development, variants of the fourth zinc finger (ZF4) WT1 are a relatively common cause of XX male development, where the gonads are testes or ovotestes. This article is typical of our interaction with clinical geneticists, where our studies on the mouse, including generating models of human disorders, provide valuable insight into conditions affecting patients, as well as revealing novel insights into the underling mechanisms.

Veronica Moncho-Amor, Probir Chakravarty, Christophe Galichet, Ander Matheu, Robin Lovell-Badge*and Karine Rizzoti*. (2021) *SOX2 is required independently in both stem and differentiated cells for pituitary tumorigenesis in p27 null mice* Proceedings of the National Academy of Sciences of USA 118 (7), e2017115118. DOI: https://doi.org/10.1073/pnas.2017115118
Tumour development depends on cell intrinsic dysfunction, but extrinsic factors can also be important drivers. Deletion of *p27*, which is downregulated in many tumours, predominantly gives pituitary tumours in mice. *Sox2*, which is transcriptionally derepressed in the absence of P27, is also important for tumorigenesis in this and other systems. Using various approaches, we establish the regulatory interaction *in vivo* of SOX2 and p27 and show that SOX2 is required independently, both cell-autonomously in the endocrine cells that form the tumours and non-cell-autonomously, in adjacent pituitary stem cells, to orchestrate tumorigenesis in the absence of P27.