BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Douglas Roland Higgs	Emeritus Professor of Haematology
eRA COMMONS USER NAME (credential, e.g., agency login)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
King's College Hospital Medical School, London UK	MB, BS	1974	
Royal College of Physicians, London, UK	MRCP	1976	
Royal College of Pathologists, London, UK	MRCPath	1983	
	DSc (Med)	1990	

A. Personal Statement

Douglas Higgs (FRS) qualified in Medicine at King's College Hospital Medical School in 1974 and trained as a haematologist. I joined the MRC Molecular Haematology Unit (Oxford) in 1977 and I was Professor of Haematology at the University of Oxford, Director of the MRC Molecular Haematology Unit and Director of the Weatherall Institute of Molecular Medicine until Spring 2020. Our current areas of interest are (i) to understand the processes by which stem cells undergo lineage commitment in haematopoiesis; (ii) to understand how genes are activated and repressed during normal haematopoiesis; (iii) to study the human genetic diseases affecting these processes. The main interest of my own laboratory has been to understand how the globin genes are regulated during haematopoiesis from their natural chromosomal environment in the telomeric region of 16p13.3. My group has characterised the terminal 2 Mb of chromosome 16 and concentrated on understanding how globin gene expression is influenced by the transcriptional programme and epigenetic modifications of this region (e.g. chromatin structure and conformation, histone acetylation, methylation, timing of replication, nuclear positioning). This work contributes to our understanding of the normal process of blood formation and provides an unusually well characterised model for understanding the mechanisms underlying mammalian gene regulation within the context of its normal chromosomal environment. I have previously supervised 30 graduate students, and numerous laboratory visitors. In addition, I have trained over 30 postdoctoral Fellows and Clinical Training Fellows. I regularly examine PhD and DPhil theses (approximately 2-3 per year for the past 25 years).

B. Positions and Honors

Positions and Employment

1975 House Physician to Dr. S. Oram and Dr. D. Jewitt, King's College Hospital.
1975 House Surgeon to Mr. E.R. Howard, King's College Hospital.
1975 SHO Neurology (locum), Professor D. Marsden, King's College Hospital.
1975 SHO Haematology to Professor J.M. White, King's College Hospital.
1976 Registrar in Haematology to Professor J.M. White, King's College Hospital.
1977 MRC Training Fellowship and Honorary Registrar, Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford.
1980 Scientific Officer (Clinical) MRC Molecular Haematology Unit, and Honorary Senior Registrar in the Nuffield Department of Clinical Medicine.
1985 Scientific Officer (Clinical), MRC Molecular Haematology Unit, and Honorary Consultant in Haematology in the Nuffield Department of Clinical Medicine.
1996 Professor of Haematology, University of Oxford. Scientific Officer (Clinical), MRC Molecular Haematology Unit, and Honorary Consultant in Haematology in the Department of Cellular Science.
2000 Director of the MRC Molecular Haematology Unit, Oxford
2005 Deputy Director of Weatherall Institute of Molecular Medicine
2012 Director of Weatherall Institute of Molecular Medicine
2020 Emeritus Professor of Haematology

Other Experience and Professional Memberships

1980 - 1984 Junior Research Fellow, Wolfson College, Oxford
1984 - British Society of Haematology
1984 - Examiner for the degree of D. Phil (Oxford University)
1985 - Member of the Association of Physicians of Great Britain and Ireland
1989 - 1996 University Research Lecturer (University of Oxford)
1996 - 1999 Editorial Board of Human Molecular Genetics
1997 - 2000 Scientific Advisory Board (Leukaemia Research Fund)
1997 Aggeler Lectureship UCSF, USA
2001 Scientific Advisory Board (Inserm, France)
2003 Member of MRC Physiological Medicine & Infections Board
2003 Member of the Patel Stem Cell Steering Committee
2005 Active Member of the New York Academy of Sciences
2007 - 2011 Associate Editor, *Blood*
2008 Member of the ASH International Members Committee
2008 Member of the *Epigenomics* Editorial Board
2009 Member of the *Molecular and Cellular Biology* Editorial Board
2009 - 2013 Member of the MRC Translational Stem Cell Research Committee
2010 BRC Scientific Advisory Board
2010 - 2016 Member of the Sir Jules Thorn Trust
2011 Governor of the Lister Institute
2011 Wellcome Trust Investigator Award Panel
2011 Director of Blood Theme for the Oxford NIHR/BRC
2012 Member of the Radcliffe Department of Medicine Committee
2012 Royal Society Wolfson Research Merit Awards Panel
2012 Doris Duke Charitable Foundation
2015 American Society of Haematology
2016- 2019 Chairman of the Sir Jules Thorn Trust

Honors

1993 F.R.C.P.
1994 F.R.C.Path.
2001 F.Med.Sci.
2004 Ham-Wasserman Lecturer (American Society of Hematology)
2005 F.R.S.
2005 The Carter Medal (British Society for Human Genetics)
2009 The British Society of Haematology Gold Medal (British Society of Haematology)
2009 Platinum Award Clinical Excellence
2010 The Alexander Weiner Lecture (New York Blood Center)
2011 The José Carreras Award (European Hematology Association)
2012 The Paul Polani Lecture (King's College, London)
2012 Doris Duke Charitable Foundation
2013 The Almroth Wright Lecture (Imperial College, London)
2013 The Buchanan Medal (The Royal Society)
2015 Gold Award Clinical Excellence
2015 - 2019 Member of the ASH® Scientific Committee
2016 - 2019 Chairman, Medical Advisory Committee, Sir Jules Thorn Charitable Trust

C. Contributions to Science

Higgs, D.R., Aldridge, B.E., Lamb, J., Clegg, J.B., Weatherall, D.J., Hayes, R.J., Grandison, Y., Lowrie, Y., Mason, K.P., Serjeant, B.E. and Serjeant G.R. The interaction of α-thalassaemia and homozygous sickle cell disease. *New Eng J Med* (1982), 306, 1441-1446.

Higgs, D.R., Goodbourn, S.E.Y., Lamb, J., Clegg, J.B., Proudfoot, N.J. and Weatherall, D.J. α thalassaemia due to a polyadenylation signal mutation. Nature (1983), 306, 398-400.

Lamb, J., Harris, P.C., Lindenbaum, R.H., Reeders, S.T., Wilkie, A.O.M., Buckle, V.J., Barton, N.J., Weatherall, D.J. and Higgs, D.R. Detection of breakpoints in submicroscopic chromosomal translocation, illustrating an important mechanism for genetic disease. Lancet (1989), ii, 819-824.

Higgs, D.R., Wood, W.G., Jarman, A.P., Sharpe, J., Lida, J., Pretorius, I-M. and Ayyub, H. A major positive regulatory region located far upstream of the human α-globin gene locus. Genes and Development, (1990), 4, 1588-1601.

Wilkie, A.O.M., Lamb, J., Harris, P.C., Finney, R.D. and Higgs, D.R. A truncated human chromosome 16 associated with α thalassaemia is stabilized by addition of telomeric repeat $(TTAGGG)_n$. Nature (1990), 346, 868-871.

Vyas, P., Vickers, M.A., Simmons, D.L., Ayyub, H., Craddock, C.F. and Higgs, D.R. Cis-acting sequences regulating expression of the human α-globin cluster lie within constitutively open chromatin. Cell, (1992), 69, 781-793.

European Polycystic Kidney Disease Consortium. The polycystic kidney disease 1 gene encodes a 14 kb transcript and lies within a duplicated region on chromosome 16. Cell, (1994), 77, 881-894.

Gibbons, R.J., Picketts, D.J., Villard, L. and Higgs, D.R. Mutations in a putative global transcriptional regulator cause X-linked mental retardation with α-thalassemia (ATR-X Syndrome). Cell (1995), 80, 837-845.

Flint, J., Thomas, K., Micklem, G., Raynham, H., Clark, K., Doggett, N.A., King, A. and Higgs, D.R. The relationship between chromosome structure and function at a human telomeric region. Nature Genetics, (1997), 15, 252-257.

Gibbons, RJ, McDowell TL, Raman S, O'Rourke DM, Garrick D, Ayyub H & Higgs DR. (2000) Mutations in *ATRX*, encoding a SWI/SNF-like protein, cause diverse changes in the pattern of DNA methylation. *Nat Genet* **24**, 368-371

Tufarelli C, Sloane-Stanley JA, Garrick D, Sharpe JA, Ayyub H, Wood WG & Higgs DR. Transcription of antisense RNA leading to gene silencing and methylation as a novel cause of human genetic disease. *Nat Genet*, (2003) 34:157-165

Hughes, J.R., Cheng, J.F., Ventress, N., Prabhakar, S., Clark, K., Anguita, E., De Gobbi, M., de Jong, P., Rubin, E. & Higgs, D.R. (2005) Annotation of cis-regulatory elements by identification, subclassification, and functional assessment of multispecies conserved sequences. *Proc Natl Acad Sci U S A,* **102,** 9830-9835.

De Gobbi, M., Viprakasit, V., Hughes, J.R., Fisher, C., Buckle, V.J., Ayyub, H., Gibbons, R.J., Vernimmen, D., Yoshinaga, Y., de Jong, P., Cheng, J.F., Rubin, E.M., Wood, W.G., Bowden, D. & Higgs, D.R. (2006). A regulatory SNP causes a human genetic disease by creating a new transcriptional promoter. *Science*, **312**, 1215-1217.

Wallace, H.A., Marques-Kranc, F., Richardson, M., Luna-Crespo, F., Sharpe, J.A., Hughes, J., Wood, W.G., Higgs, D.R. & Smith, A.J. (2007) Manipulating the mouse genome to engineer precise functional syntenic replacements with human sequence. *Cell*, **128**, 197-209.

Vernimmen, D., Gobbi, M.D., Sloane-Stanley, J.A., Wood, W.G. & Higgs, D.R. (2007) Long-range chromosomal interactions regulate the timing of the transition between poised and active gene expression. *EMBO J.* **26**, 2041-2051.

Lower, K.M., Hughes, J.R., De Gobbi, M., Henderson, S., Viprakasit, V., Fisher, C., Goriely, A., Ayyub, H., Sloane-Stanley, J., Vernimmen, D., Langford, C., Garrick, D., Gibbons, R.J. & Higgs, D.R. (2009) Adventitious changes in long-range gene expression caused by polymorphic structural variation and promoter competition. *Proc Natl Acad Sci U S A,* **106,** 21771-21776.

Goldberg, A.D., Banaszynski, L.A., Noh, K.-M., Lewis, P.W., Elsaesser, S.J., Stadler, S., Dewell, S., Law, M., Guo, X., Li, X., Wen, D., Chapgier, A., DeKelver, R.C., Miller, J.C., Lee, Y.-L., Boydston, E.A., Holmes, M.C., Gregory, P.D., Greally, J.M., Rafii, S., Yang, C., Scambler, P.J., Garrick, D., Gibbons, R., Higgs, D.R., Cristea, I.M., Urnov, F.D., Zheng, D. & Allis, C.D. (2010) Distinct factors control histone variant H3.3 localization at specific genomic regions. *Cell,* **140,** 678-691.

Law, M.J., Lower, K.M., Voon, H.P., Hughes, J.R., Garrick, D., Viprakasit, V., Mitson, M., De Gobbi, M., Marra, M., Morris, A., Abbott, A., Wilder, S.P., Taylor, S., Santos, G.M., Cross, J., Ayyub, H., Jones, S., Ragoussis, J., Rhodes, D., Dunham, I., Higgs, D.R. & Gibbons, R.J. (2010) ATR-X syndrome protein targets tandem repeats and influences allele-specific expression in a size-dependent manner. *Cell* **143**, 367-378.

Kowalczyk, M.S., Hughes, J.R., Garrick, D., Lynch, M.D., Sharpe, J.A., Sloane-Stanley, J.A., McGowan, S.J., De Gobbi, M., Hosseini, M., Vernimmen, D., Brown, J.M., Gray, N.E., Collavin, L., Gibbons, R.J., Flint, J., Taylor, S., Buckle, V.J., Milne, T.A., Wood, W.G. & Higgs, D.R. (2012) Intragenic Enhancers Act as Alternative Promoters. *Molecular cell,* **45,** 447-458.

Hughes, J.R., Roberts, N., McGowan, S., Hay, D., Giannoulatou, E., Lynch, M., De Gobbi, M., Taylor, S., Gibbons, R. & Higgs, D.R. (2014) Analysis of hundreds of cis-regulatory landscapes at high resolution in a single, high-throughput experiment. *Nature genetics,* **46,** 205-212.

Hay (2016) Genetic dissection of the alpha-globin super-enhancer in vivo. *Nat Genet,* **48,** 895

Hanssen, L.L.P., Kassouf, M.T., Oudelaar, A.M., Biggs, D., Preece, C., Downes, D.J., Gosden, M., Sharpe, J.A., Sloane-Stanley, J.A., Hiughes, J.R., Davies, B. & Higgs, D.R. (2017) Tissue-specific CTCF-cohesin-mediated chromatin architecture delimits enhancer interactions and function in vivo. *Nat Cell Biol*, **19**, 952-961.

Mettananda, S., Fisher, C.A., Hay, D., Badat, M., Quek, L., Clark, K., Hublitz, P., Downes, D., Kerry, J., Gosden, M., Telenius, J., Sloane-Stanley, J.A. Faustino, P., Coelho, A., Doondea, J., Usukhbayar, B., Sopp, P., Sharpe, J.A., Hughes. J., Vyas, P., G.ibbons, R.J. & Higgs, D.R. (2017) Editing an α-globin enhancer in primary human hematopoietic stem cells as a treatment for β-thalassemia. *Nat Commun*, **8**, 424.

Oudelaar, A.M., Davies, J.O.J., Hanssen, L.L.P., Telenius, J.M., Schwessinger, R., Liu, Y., Brown, J.M., Downes, D.J., Chiariello, A.M., Bianco, S., Nicodermi, M., Buckle, V.J., Dekker, J. & Higgs, D.R. (2018) Single-allele chromatin interactions identify regulatory hubs in dynamic compartmentalized domains.. *Nat Genet*, **50**, 1744-1751.

Ongoing Research Support

MRC Unit Programme Grant – 01 April 2017 – 31 March 2022. Core funding for the MRC Molecular Haematology Unit

MRC Programme grant within MRC Molecular Haematology Unit "The regulation of globin gene expression during haemopoiesis" - 01 April 2017 – 31 March 2022. Core funding for the MRC Molecular Haematology Unit. Role: PI

MRC Programme grant within MRC Molecular Haematology Unit "Characterisation of ATRX, a chromatin remodelling protein" - 01 April 2017 – 31 March 2022. Core funding for the MRC Molecular Haematology Unit. Role: PI

Oxford NIHR BRC Blood Theme - 01 April 2017 – 31 March 2022. Role: Theme leader for this research activity

The Oxford Single Cell Biology Consortium – John Fell Fund – 01 May 2016 – 31 March 2019. Role: Lead PI

NIH – National Institutes of Health USA – 01 May 2015 – 30 April 2020. Accelerating Medicine Partnership (AMP) in type 2 diabetes. Role: Co-PI

WT – Wellcome Trust PhD Studentship – Caroline Harrold - 01 October 2015 – 30 September 2019. £161,673. 109110/Z/15/Z Role: Co-Supervisor (with J Hughes)

Wellcome Trust Four-Year PhD Studentship – Helena Francis - Functional dissection of a single enhancer sequence at the mouse α-globin locus. - 01 Oct 2015 – 30 Sept 2019. £199,256. Role: Supervisor

MRC Strategic Alliance Funding. - 01 April 2015 – 31 March 2020. £3,808,129. Role: PI

NIH – National Institutes of Health USA. Accelerating Medicine Partnership (AMP) in type 2 diabetes. 01 May 2015 – 30 April 2020. £917,526.11. Role: Co-PI (with M. McCarthy)

NIH – National Institutes of Health USA. VISION.. 01 July 2016 – 01 July 2021. £247,699. Role: Co-PI (with J Hughes)

Medical Research Council Clinical Research Training Fellowship – Mohsin Badat - Development of a novel therapy for beta-thalassaemia using CRISPR/Cas9 to edit the major alpha-globin enhancer.. 05 Sept 2017 – 04 Sept 2020. £253,742. Role: Co-Supervisor (with R Gibbons)

Medical Research Council Clinical Research Training Fellowship – Asger Jakobsen. Molecular and cellular basis of clonal dominance in myeloid malignancy,. 03 October 2017 – 02 October 2020. £254,102. Role: Co-Sponsor (with P Vyas)

Wellcome Trust: ISSF – Institutional Strategic Support Fund. The Oxford Quantitative Biology Training Programme. 01 June 2018 – 31 May 2021. £100,000. Role: Lead PI

Completed Research Support

MRC Unit Programme Grant – 01 April 2012 – 31 March 2017. Core funding for the MRC Molecular Haematology Unit

MRC Programme grant within MRC Molecular Haematology Unit "The regulation of globin gene expression during haemopoiesis" - 01 April 2012 – 31 March 2017. Core funding for the MRC Molecular Haematology Unit. Role: PI

Oxford NIHR BRC Blood Theme (Theme Leader) – 01 April 2007 – 31 March 2012. Research leader to develop translational research in haematology: Theme leader

Wellcome Trust Training Fellowship in Biomedical and Clinical Sciences Dr Deborah Hay, - 01 July 2009 – 30 June 2012 The role of distal regulatory elements in α-globin transcription. Role: Co-supervisor (with R Gibbons)

Wolfson Imaging Bid - awarded 2011. Developing a new imaging infrastructure Role: Co-PI (with Enzo Cerundolo)

MRC Centenary Award - 01 April 2012 – 31 March 2017. Core funding for the MRC Weatherall Institute of Molecular Medicine. Role: PI

Wellcome Trust Strategic Award – 01 January 2015 – 31 December 2018. A systemic approach to understanding the biology underpinning GWAS hits. Role: Co-PI

WT Institute Strategic Support Fund – 01 October 2014 – 30 September 2018. Role: Co-PI

MRC Research Grant: MICA – Nanoscopy Oxford (NanO): - 01 January 2013 – 31 December 2017. Novel Super-Resolution Imaging Applied to Biomedical Sciences. Role: Co-PI (with I Davis)

Wellcome Trust ISSF – 01 April 2014 – 31 October 2017. Single Cell biology in Oxford. Role: PI

MRC-University Translational Medicine – 01 April 2010 – 30 September 2017. Role: PI