## Douglas Higgs

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|  | **Prof Doug Higgs**  **Titles**: Professor of Haematology  **Location**: MRC Weatherall Institute of Molecular Medicine  **Department**: Radcliffe Department of Medicine  **Group**: Laboratory of Gene Regulation  **Webpage**: https://www.imm.ox.ac.uk/people/doug-higgs  **Email**: doug.higgs@imm.ox.ac.uk  **PA**: liz.rose@imm.oc.ac.uk |

**Research Overview:**

I am currently Professor of Molecular Haematology at the University of Oxford and until recently Director of the MRC Molecular Haematology Unit (MHU). I was also Director of the MRC Weatherall Institute of Molecular Medicine (WIMM) at the University of Oxford (2012-2020). I am both clinically qualified (FMedSci) and scientifically active (FRS and member of EMBO) and currently run an internationally leading research laboratory studying the regulation of gene expression.

### GMS themes:

* Genomic and –omic technologies
* Functional genomics
* Genome biology (genomes and genetic variation)
* Genomics of disease
* Genomic analysis (bioinformatics and statistical genetics)
* From genes to clinic (target discovery, structural biology, medicinal chemistry)
* Application of genomics in the clinic (diagnostics and therapeutics)

**Research Focus**

Our laboratory is interested in the general question of how mammalian genes are switched on and off during lineage commitment and differentiation. We use the most recent genomics technologies to study individual genes in detail and study gene expression using genome-wide analyses. We study all aspects of gene expression including the key cis-regulatory elements (enhancers, promoters and insulators), the transcription factors and co-factors that bind them, the epigenetic modifications of chromatin and DNA and the role of associated phenomena such as chromosome conformation and nuclear sub-compartmentalisation using imaging techniques. These studies are performed both in cell systems and in model organisms as well as in human patients with various inherited and acquired genetic and epigenetic abnormalities. We use all aspects of computational biology including machine learning to extract general biological principles from our genomic datasets.  The translational goal of our work is to develop new ways to modify gene expression during blood formation with the aim of manipulating gene expression and ameliorating the clinical phenotypes of patients with a variety of blood disorders.

**Some recent references from our laboratory**

Hughes JR, Roberts N, McGowan S, Hay D, Giannoulatou E, Lynch M, de Gobbi M, Taylor S, Gibbons R & **Higgs DR** Analysis of hundreds of cis-regulatory landscapes at high resolution in a single, high-throughput experiment. *Nat Genet*, (2014).

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Oudelaar AM, Davies JOJ, Hanssen LLP, Telenius JM, Schwessinger R, Liu Y, Brown JM, Downes DJ, Chiariello AM, Bianco S, Nicodemi M, Buckle VJ, Dekker J, **Higgs DR** & Hughes JR Single-allele chromatin interactions identify regulatory hubs in dynamic compartmentalized domains. *Nat Genet*, (2018).

Larke MSC, Schwessinger R, Nojima T, Telenius J, Beagrie RA, Downes DJ, Oudelaar AM, Truch J, Graham B, Bender MA, Proudfoot NJ, **Higgs DR**, Hughes JR. Enhancers predominantly regulate gene expression during differentiation via transcription initiation. Mol Cell. 2021

Hua P, Badat M, Hanssen LLP, Hentges LD, Crump N, Downes DJ, Jeziorska DM, Oudelaar AM, Schwessinger R, Taylor S, Milne TA, Hughes JR, **Higgs DR,** Davies JOJ. Defining genome architecture at base-pair resolution. Nature. 2021

**Project areas**: gene regulation, epigenetics, chromatin structure and function, computational biology.

### Specific project proposals:

Determining the grammar and syntax of regulatory elements using laboratory and computational approaches

Please contact directly for further information.

*These pages were reviewed/updated:* ***[27th July 2021]***

Project proposal

**Title: Determining the grammar and syntax of regulatory elements using laboratory and computational approaches**

**Supervisors:** Professor Doug Higgs, Professor Jim Hughes

Wet/dry lab mix: ~50% wet lab, ~50% dry lab

Description:

A major goal of current biology is to understand how DNA sequences are read by the nuclear machinery to direct normal development and differentiation and how this is perturbed in human disease. Whole genome sequences of a wide range of organisms spanning 500 million years of evolution are now available for detailed analysis. We currently know that there are ~20,000 structural genes in humans but their expression is regulated by as many as 1,000,000 regulatory elements including enhancers, promoters and boundary elements. Of particular interest, enhancers integrate external cell signals with the internal transcriptional and epigenetic programmes and communicate this information to their cognate promoters thereby controlling when and where specific genes are switched on and off. Many single genes are controlled via clusters of enhancers which are each bound by a variety of cell specific and general transcription factors which relay information from enhancers to promoters. Although structural genes are in general well conserved, the positions and DNA sequences of regulatory elements which control their expression change quite rapidly throughout evolution.

These observations beg the question of how the precise timing and cell-specific expression of a particular gene is maintained in the face of such dramatic changes in the regulatory elements? This question gets to the heart of our lack of understanding of the mechanism by which enhancers communicate with promoters. If regulatory elements can change so much during evolution how is specific information passing from enhancers to promoters encoded? We will study this key issue by initially studying the well characterised alpha globin locus as a model. The globin genes are expressed in a very similar developmental and tissue-specific manner in diverse species spanning 500 million years of evolution and the structure of the genes encoding the globin proteins is well conserved. By contrast, the cluster of enhancers (so called super-enhancer) controlling their expression varies considerably. Using a combination of established lab-based assays together with extensive computational analysis of the regulatory elements we will initially determine how the positions and sequences of the regulatory elements have evolved in a wide variety of species including fish, amphibians, birds and mammals including a wide range of primates. Based on our consequent understanding of the evolution of globin gene regulation, we will extend and generalise these observations to other enhancers throughout the genome.

**Training Opportunities:** Our laboratory of ~12-14 scientists, includes post-docs, students and research assistants. Students undertaking their studies in the lab have day-to-day supervision from a team of scientists who have considerable experience in all aspects of current genomics including, for example, RNA-seq, ATAC-Seq, ChIP-seq, and various forms of chromosome conformation capture. We also have considerable expertise in cell biology and imaging. A key aspect of our work in collaboration with the WIMM Centre for Computational Biology involves a full range of analytical approaches using computational biology.

**References**

**The Tree of Life Project:** [**https://www.sanger.ac.uk/programme/tree-of-life/**](https://www.sanger.ac.uk/programme/tree-of-life/)

Oudelaar AM, Higgs DR. The relationship between genome structure and function. Nat Rev Genet. 2021 Mar;22(3):154-168. doi: 10.1038/s41576-020-00303-x.

Oudelaar AM, Beagrie RA, Kassouf MT, Higgs DR. The mouse alpha-globin cluster: a paradigm for studying genome regulation and organization. Curr Opin Genet Dev. 2021 Apr;67:18-24. doi: 10.1016/j.gde.2020.10.003.

Buffry AD, Mendes CC, McGregor AP. The Functionality and Evolution of Eukaryotic Transcriptional Enhancers. Adv Genet. 2016;96:143-206. doi: 10.1016/bs.adgen.2016.08.004.