PI profile

## Jim Hughes

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| A person in a black shirt  Description automatically generated with medium confidence | **Professor Jim Hughes****Titles**: Professor of Gene Regulation, Group Leader / PI**Location**: MRC Weatherall Institute of Molecular Medicine**Department**: Radcliffe Department of Medicine **Group**: Hughes Group: Genome Biology**Webpage**: <https://www.imm.ox.ac.uk/people/jim-hughes>**Email**: jim.hughes@imm.ox.ac.uk |

### GMS themes:

[Please retain any that describe your research, deleting others:]

* Genomic and –omic technologies
* Functional genomics
* Genome biology (genomes and genetic variation)
* Genomics of disease
* Genomic analysis (bioinformatics and statistical genetics)

### Research Overview

The Hughes group is interested in how mammalian genes are regulated and how their deregulation is linked with human disease. The ~22 thousand genes in the mammalian genome are present in the DNA of every cell but are used in complex patterns in different cell types and organs. This system to turn genes off or on, modulating their levels of activity in different cell types is central to maintaining the complex biological system that is a multicellular organism.

What has become clear from large-scale genetic studies of human predisposition to common disease is that it is the control of the use of genes, rather than the genes themselves, that is frequently damaged. It is now known that functional elements other that genes exist in our DNA and these elements act as molecular switches which interact with the genes and control their use, however the mechanisms involved are not well understood. The Hughes group integrates both bench technologies and computational approaches to try and understand how these regulatory switches or enhancer elements work and how variations in their activity in our genomes leads to increased risk of developing common diseases, such as anemia, cancer, diabetes and autoimmune diseases.

The group has a track history in the development of novel genomics technologies as well as computational approaches. The group has a molecular biology arm that is expert in next-generation sequencing based genomics and a purely computational arm which forms part of the WIMM CCB computational unit, with many lab members working in both areas. Due to this structure, the group is highly multi-disciplinary, including people from diverse backgrounds and skill sets, from nucleic acid chemistry, biochemistry and molecular biology to bioinformatics, deep neural networks and JavaScript programmers and is always keen to incorporate new approaches from different fields to help answer its central questions.

Project areas:

Genomics and Machine Learning.

Synthetic biology and gene regulation.

Sequence variation and disease.

Single cell multi-omics and sequence variation.

### Project proposal

Supervisors: Professor Jim Hughes

**Title**: Various computational and bench projects

Wet/dry lab mix: varies

**Description**:

The group has opportunities for purely computational projects and bench projects although bench scientists are strongly encouraged and trained to do their own bioinformatic analysis and develop their own coding skills.

Computational projects combine the integration of genomics data, including single cell epigenomic and transcriptomic data, with the development of machine learning based approaches to predict fundamental aspects of gene regulation in the mammalian genome. The ultimate goals of these projects are to use the deep neural network based approaches to understand the basic principles of how cell type specific gene regulation is achieved and to provide predictive platforms to identify casual changes in the non-coding genome and to identify the underlying mechanism and genes linked to human disease.

Relevant publications.

* Schwessinger, R., et al (2017). Sasquatch: predicting the impact of regulatory SNPs on transcription factor binding from cell- and tissue-specific DNase footprints*.* *Genome Res*. 27: 1730-1742.
* Schwessinger, R., et al. (2020). DeepC: predicting 3D genome folding using megabase-scale transfer learning*.* *Nat Methods*. **17**: 1118-1124.
* Downes, D.J., et al (2019)**.** An integrated platform to systematically identify causal variants and genes for polygenic human traits*.* *bioRxiv*: 813618.

Bench projects involve using the latest genomics technologies, including those developed by the group to understand the basic regulation of genes and the impact of sequence variation on it. The group is expert in chromosome conformation capture technologies and have developed the suite of Capture-C technolgies (Capture-C, Tiled-C and Tri-C) used to interogate the regulatory landcapes of genes. Projects include using these and high-resolution variants such as Micro Capture-C (with J Davies) in primary cells to understand the effect of human variation on specific genes and en masse to understand basic principles. The group also leaverges large-scale synthetic biology to build regulatory domains from first principles (<https://www.thedarkmatterproject.org/main>) to discover the principles of how they are built and to provide a practical toolkit to build and exploit functional bespoke gene regulatory domains in the mammalian genome. Projects also exist to develop new methods to fill in our current “blindspots” in our ability to assess activity and function in the genome.

Relevant publications.

* Larke, M.S.C., et al**.** (2021). Enhancers predominantly regulate gene expression during differentiation via transcription initiation*.* *Mol Cell*. **81**: 983-997 e7.
* Oudelaar, A.M., et al**.** (2018). Single-allele chromatin interactions identify regulatory hubs in dynamic compartmentalized domains*.* *Nat Genet*.
* Oudelaar, A.M., and Beagrie, R.A., et al (2020). Dynamics of the 4D genome during in vivo lineage specification and differentiation*.* *Nat Commun*. **11**: 2722
* Hua, P., et al (2021). Defining genome architecture at base-pair resolution*.* *Nature*. **595**: 125-129.

Please contact directly for further information.

*These pages were reviewed/updated:* ***[23-07-21]***

Insert any additional project description(s) on subsequent pages if applicable. Please use the same template and use separate pages for each project.