Name	GREGORY FINDLAY
Position	Group Leader (1st 6)
Year joined *(Crick or founder institute)*	2020

Career History

2012-2020: University of Washington Medical Scientist Training Program (M.D./Ph.D.)
May 2020: M.D.- University of Washington, School of Medicine
March 2018: Ph.D. University of Washington, Genome Sciences, lab of Dr. Jay Shendure

Major Awards, Honours and Prizes

2021: Named to Clinical Omics “Pioneers Under 40” List
2019: Western Association of Graduate Schools ‘Innovation in Technology’ Thesis Award
2016: Awarded an NIH F30 Individual Fellowship for MD/PhD training
2014-2017: University of Washington ARCS Foundation Scholar

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

Member of the Atlas of Variant Effect Alliance, from 2020

Lab Name	***Genome Function Laboratory***

Research programme and achievements

The Genome Function Laboratory develops methods to understand genetic differences and the effects they can have on a person’s life and health.

The DNA sequence of the human genome is nearly identical between any two people, yet each person also has millions of genetic variants that make their genome unique. With current DNA sequencing technology, we can readily find the set of rare genetic variants present in each individual, yet it remains hugely challenging to predict how each variant will impact health. In the context of certain diseases like cancer and heart disease, recognising a deleterious mutation in a patient early can guide interventions that prolong life expectancy by many years. This clinical need to understand the effects of variants, coupled with a basic desire to understand the diversity of functions encoded in the human genome, motivates the lab to systematically study genetic variants with a particular focus on tumour suppressor genes.

1. One method we developed called “Saturation Genome Editing” allows us to test the effects of all possible single nucleotide variants across key regions of the human genome. We applied this method to a gene linked to breast and ovarian cancer called *BRCA1*, testing thousands of different variants. Hundreds of these had been previously seen in people, yet their health consequences were largely unknown. Now that we have clear evidence as to whether or not these variants are likely to cause cancer, many patients are getting more accurate diagnoses. We are now applying Saturation Genome Editing to four additional genes in which mutations cause different tumours, with the goal of being better able to predict disease occurrence and treatment response from knowledge of variant effect.

2. A second genome editing technology we previously developed called ScanDel allows us delete thousands of different genomic regions at once to better understand how each one functions and to discover regulatory elements. These high-throughput CRISPR experiments can reveal the logic behind how our genes are regulated and promise to shine light on new therapeutic strategies.

3. We are developing more highly scalable methods that will allow us to engineer and test millions of human variants using the newest genome editing tools, including “prime editing” and “base editing” systems. We hope to apply artificial intelligence to these large experimental data sets as a means of modelling variants’ effects on diverse molecular processes genome-wide.

4. To date, the high-throughput methods we and others use are limited in the depth of information provided about each variant assayed. Future work in the group will couple single-cell genomics approaches to the multiplex genome editing strategies outlined above to reveal in exquisite detail what effects a variant has on processes such as splicing and transcriptional activity genome-wide. We predict this work will allow us to characterise many cancer-relevant mutations whose effects are hard to study through more limited experimental systems.

Together, these experiments will help usher in an era of precision medicine in which understanding a patient’s genetic differences leads directly to better healthcare. Importantly, our research will help democratise this growing field by providing patients of all genetic backgrounds with high-quality data.

Research outputs

Findlay, G.M., et al. (2018). ***Accurate classification of BRCA1 variants with saturation genome editing.*** **Nature, 562, 217–222. DOI:** [10.1038/s41586-018-0461-z](https://doi.org/10.1038/s41586-018-0461-z)
This work was the first to demonstrate how saturation mutagenesis of critical genomic regions can be used to classify variants seen clinically with great accuracy. We engineered thousands of variants in *BRCA1* to ask how each one impacts gene function and RNA expression in human cells. Our “function scores” for each mutation tested achieved near-perfect accuracy (>97%) for predicting pathogenicity, thus establishing an experimental paradigm for adjudicating variant effects applicable to hundreds of genes harbouring thousands of variants likely to be consequential to health and disease.

McKenna, A., Findlay, G.M., et al. (2016). ***Whole-organism lineage tracing by combinatorial and cumulative genome editing*****. Science 353, aaf7907. DOI: 10.1126/science.aaf7907**
This paper marks the first use of CRISPR/Cas9 genome editing as a means of cellular lineage tracing. We deploy the method to tag over a thousand unique embryonic lineages in zebrafish and relate them to one another by patterns of shared mutations. This information allows us to quantitatively study the complex lineage relationships between hundreds of thousands of cells sampled across entire adult organisms.

Findlay, G.M., et al. (2014). ***Saturation editing of genomic regions by multiplex homology-directed repair.*** **Nature 513, 120–123. DOI: 10.1038/nature13695**
This paper introduces saturation genome editing (SGE). In this method, a multiplex homology-directed repair step is used to introduce thousands of programmed variants at a single genomic locus of interest. Next-generation sequencing is then used as a means of deciphering the variants' effects on processes such as splicing and protein activity.