BIOGRAPHICAL SKETCH

NAME: Frederick P. Roth

POSITION TITLE: Professor and Chair

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completed	FIELD OF STUDY
University of California, Berkeley, CA	B.A.	Dec 1990	Physics and Molecular & Cell Biology
Harvard University, Cambridge, MA	Ph.D.	Jun 1998	Biophysics

A. Personal Statement

My team develops and applies experimental and computational genomic technology, and trains multidisciplinary and collaborative scientists, including 14 PhD and 20 postdoc alums to date. Our primary research focus is on generating comprehensive experimental maps of functional sequence variation ('variant effect maps') and establishing their clinical utility. To date, we have generated variant effect maps for over 20 human proteins using highly-multiplexed cell-based assays. For several of these, we have generated maps under multiple environments, genetic contexts or assays. Members of my team serve on multiple ClinGen working groups and variant curation expert panel to enable translation of variant effect maps for clinical use.

B. Positions, Scientific Appointments, and Honors

Selected Positions

2023 – present Professor and Chair, Department of Computational & Systems Biology, University of Pittsburgh School of Medicine.

2011 - 2023 Professor, University of Toronto, Donnelly Centre for Cellular & Biomolecular Research and Departments of Molecular Genetics and Computer Science

2011 - 2023 Senior Investigator, Lunenfeld-Tanenbaum Research Institute, Sinai Health, Toronto, ON

2000 - 2010 Assistant Professor (2000 – 2007) and Associate Professor (2007 – 2010), Harvard Medical School, Dept of Biological Chem and Mol Pharmacology, Boston, MA

1998 - 2000 Scientist, Millennium Pharmaceuticals, Predictive Medicine Bioinformatics Group, Cambridge, MA (w/ Dr. Chris Sander)

1992 - 1998 Graduate Student, Harvard University Graduate Biophysics Program and Harvard Med School Dept of Genetics, Boston, MA (w/ Dr. George Church)

1991 - 1992 Staff Scientist, Operon Technologies, Inc., Alameda, CA

Summer 1990 Research Fellow, Scripps Inst. of Oceanography, San Diego, CA

Summer 1989 Research Assistant, UC Berkeley, Dept of Molecular & Cell Biology

1987 - 1990 Research Assistant, Space Sciences Lab, Berkeley, CA

1987 Research Assistant, Fly's Eye Cosmic Ray Facility, Dept of Physics, U of Utah

Selected Scientific Roles

2023 – present Executive Committee Member, Pitt PhD Program in Integrative Systems Biology

2023 – present Executive Committee Member, Joint CMU-Pitt PhD Program in Computational Biology

2020 - 2022 Co-Director, Computational Bio Track in the Mol Genetics Grad Program, U Toronto

2017 – present Editorial Board Member, **Molecular Systems Biology**

2014 – 2020 Co-Director, Canadian Institute for Advanced Research Genetic Networks Program

2014 – 2019 Member and Chair (2017-2019), NIH Genomics, Computational Biology and Technology (GCAT) Study Section

2011 – 2016 Associate Editor, **G3: Genes|Genomes|Genetics**

2010 – 2014 Associate Editor, **PLoS Computational Biology**

2001 – 2004 Associate Editor, **Bioinformatics**

Honors

2011 – present Canada Excellence Research Chair

2008 – present Senior Fellow, Canadian Institute for Advanced Research Genetic Networks Program

1993 – 1996 National Science Foundation Graduate Fellowship

C. Contributions to Science

1. Function and disease association of genes and sequence variants: We have made many contributions to measure, infer and understand the functional and disease impacts of missense variants, e.g. via variant effect mapping in which we experimentally test the functional impacts of nearly all possible single amino acid substitutions (for ~20 genes thus far). I co-founded the Atlas of Variant Effects Alliance (an international initiative to facilitate variant effect mapping), and co-developed MaveDB, MaveQuest, MaveRegistry and other community resources related to variant effect mapping. We also developed VARITY, one of the currently-best-performing pathogenicity predictors for rare human missense variants, and have carried out unbiased assessment of computational variant effect predictors using large prospective human cohorts. In earlier work, my team has developed both machine learning and experimental methods for inferring gene functions and phenotypes, e.g., combining information from diverse systematic datasets to prioritize the most likely causal gene at GWAS loci.

a. DR Tabet*, AG Cote*, MC Lancaster, J Weile, A Rayhan, I Fotiadou,,, K Matreyek, DM Fowler, M Bourbon, SG Pfisterer, AM Glazer, BM Kroncke, VN Parikh, EA Ashley, JW Knowles, M Claussnitzer, ET Cirulli, RA Hegele, DM Roden, CA MacRae, ***FP Roth***†. The functional landscape of coding variation in the familial hypercholesterolemia gene LDLR. **Science** [First Release Oct 30] (2025). [NIHMSID:2125470]

b. W van Loggerenberg*, S Sowlati-Hashjin*, J Weile, R Hamilton,,, A Colavin, R Nussbaum, ECH Friesema, R Kauppinen, J To-Figueras, AK Aarsand, RJ Desnick‡, M Garton†‡, ***FP Roth***†‡. Systematically testing human HMBS missense variants to reveal mechanism and pathogenic variation. **American Journal of Human Genetics** 110(10):1769-1786 (2023). [PMC10577081]

c. M Gebbia*, D Zimmerman*, R Jiang, M Nguyen, J Weile, R Li, M Gavac, N Kishore, S Sun, RA Boonen, R Hamilton, JN Dines, A Wahl, J Reuter, B Johnson, DM Fowler, F Couch, H van Attikum, ***FP Roth***†. A missense variant effect map for the human tumour suppressor protein CHK2. **American Journal of Human Genetics** 111(12): 2675-2692 (2024) [PMC11639082]

d. Y Wu, R Li, S Sun, J Weile, ***FP Roth***†. Improved pathogenicity prediction for rare human missense variants. **American Journal of Human Genetics**. 108(10):1891-1906 (2021). [PMC8715197]

2. Experimental genomic technology development: Since 2010, my group has contributed to experimental genomic technology development. For example, towards mapping protein and genetic interactions, we developed the barcode fusion genetics (BFG) strategy in which the barcodes from two 'one-dimensional' barcoded yeast haploid strain libraries could be recombined to enable multiplexed study of all mated-diploid strain pairs. The BFG approach has been applied to efficiently measure both protein and genetic interactions under different environments. We also developed a combined experimental/computational TileSeq framework for deep mutational scanning to assess the functional impact of human variation.

a. N Yachie*†, E Petsalaki*, JC Mellor, J Weile, Y Jacob, M Verby, SB Ozturk, S Li, AG Cote, R Mosca, JJ Knapp, M Ko, A Yu, M Gebbia, N Sahni, S Yi, T Tyagi, D Sheykhkarimli, JF Roth, C Wong, L Musa, J Snider, Y-C Liu, H Yu, P Braun, I Stagljar, T Hao, MA Calderwood, L Pelletier, P Aloy, DE Hill, M Vidal & ***FP Roth***†. Pooled-matrix protein interaction screens using Barcode Fusion Genetics. **Molecular Systems Biology** 12(4):863 (2016). [PMC4848762]

b. Y Suzuki, RP St. Onge, R Mani, OD King, A Heilbut, VM Labunskyy, W Chen, L Pham, LV Zhang, AHY Tong, C Nislow, G Giaever, VN Gladyshev, M Vidal, P Schow, J Lehár & ***FP Roth***†. Knocking out multi-gene redundancies via cycles of sexual assortment and fluorescence selection. **Nature Methods** 8(2):159-64 (2011). [PMC3076670]

c. JJ Diaz-Mejia, JC Mellor, A Cote, A Balint, B Ho, P Bansal, F Shaeri, M Gebbia, J Weile, M Verby, A Karkhanina, Y Zhang, C Wong, J Rich, D Prendergast, G Gupta, S Ozturk, D Durocher, GW Brown, ***FP Roth***†. Mapping DNA damage-dependent genetic interactions in yeast via party mating and barcode fusion genetics. **Molecular Systems Biology** 14(5):e7985 (2018) [PMC5974512].

d. J Weile, S Sun, AG Cote, J Knapp, M Verby, JC Mellor, Y Wu, C Pons, C Wong, N van Lieshout, F Yang, M Tasan, G Tan, S Yang, DM Fowler, R Nussbaum, JD Bloom, M Vidal, DE Hill, P Aloy & ***FP***

Roth†. A framework for exhaustively mapping functional missense variants. **Molecular Systems Biology** 13(12):957 (2017). [PMC5740498]

3. Gene and drug interaction mapping and analysis: The largest contribution to the field of genetic interaction mapping is an empirical approach to guide choices on how genetic interaction should be defined. In the analysis of large-scale maps of genetic interaction, we also showed the extent to which genetic interactions can be inferred (important for human and other species where exhaustive genetic interaction mapping is not yet feasible). We adapted classical epistasis analysis for causal gene ordering with systematically-collected quantitative genetic interaction data. We developed a next-generation sequencing-based method for mapping genetic interactions in yeast, and used it to map genetic interactions under ten DNA-damaging growth conditions. We have also mapped networks of suppressor interactions in yeast and determined that they are more strongly enriched for close functional relationships than any other genetic interaction type, highlighting once again the importance of fundamental understanding for identifying therapeutic interventions. We also developed the XGA strategy to map high-order combinatorial genetic interactions. In a variant effect mapping study, we measured within-gene genetic interactions for nearly all possible missense variants in MTHFR with the common (30% global minor allele frequency) functional variant Ala222Val, concluding that clinical interpretation of MTHFR variants should be informed by genetic interactions with this common functional variant.

a. R Mani, RP St. Onge, J Hartman, G Giaever, ***FP Roth***†. Defining genetic interaction. **Proceedings of the National Academy of Sciences** 105(9):3461-3466 (2008). [PMC2265146]
b. M Cokol, HN Chua, M Tasan, B Mutlu, ZB Weinstein, Y Suzuki, ME Nergiz, M Costanzo, A Baryshnikova, G Giaever, C Nislow, CL Myers, BJ Andrews, C Boone, ***FP Roth***†. Systematic exploration of synergistic drug pairs. **Molecular Systems Biology** 7(544):1-9 (2011). [PMC3261710]
c. J van Leeuwen*, C Pons*, JC Mellor, TN Yamaguchi, H Friesen,,, M Costanzo, A-C Gingras, P Aloy, C Oostenbrink, A Murray, TR Graham, CL Myers†, BJ Andrews†, ***FP Roth***† & C Boone†. Exploring genetic suppression interactions on a global scale. **Science** 354(6312):599, aag0839-1-11 (2016). [PMC5562937]
d. A Celaj, M Gebbia, L Musa, AG Cote, J Snider, V Wong, M Ko, T Fong, P Bansal, JC Mellor, G Seesankar, M Nguyen, S Zhou, L Wang, N Kishore, I Stagljar, Y Suzuki, N Yachie† & ***FP Roth***†. Highly-combinatorial genetic interaction analysis reveals a multi-drug transporter influence network. **Cell Systems** 10(1):25-38.e10 (2020). [PMC6989212].

4. Protein interaction network mapping and analysis: We have contributed to many large-scale protein interaction mapping and analysis projects: I was a corresponding author guiding analyses of large-scale maps of *S. cerevisiae*, *C. elegans* and three successively larger reference maps of the human protein interactome. Examples of interaction analysis include the use of local network topology measures to improve inference of protein interactions and using probabilistic protein interaction networks to identify members of partially known protein complexes. We have also developed methods for 'multi-color' network motif analysis by integrating protein interactions with other relationship types. We led analysis aspects of a systematic study showing DNA tumourvirus network perturbations to be an effective way to identify cancer genes, and another characterizing the impact of Mendelian disease mutations on protein interaction. Most recently, we experimentally co-generated and analyzed a systematic map of binary (direct) interactions between human and SARS-CoV-2 proteins.

a. J-F Rual*, K Venkatesan*, T Hao, T Hirozane-Kishikawa, A Dricot, N Li, GF Berriz, FD Gibbons, M Dreze,,, L Doucette-Stamm, ME Cusick, DE Hill†, ***FP Roth***† & M Vidal†. Towards a proteome-scale map of the human interactome network. **Nature** 437:1173-1178 (2005). [PMC3057923]
b. T Rolland*, M Tasan*, B Charloteaux*, SJ Pevzner*, Q Zhong*, N Sahni*, S Yi*, I Lemmens, C Fontanillo, R Mosca, A Kamburov,,, Y Xia, A-L Barabasi, L Iakoucheva, P Aloy, J De Las Rivas, J Tavernier, MA Calderwood, DE Hill, T Hao, ***FP Roth***† & M Vidal†. A proteome-scale map of the human interactome network. **Cell** 159(5):1212-1226 (2014). [PMC4266588]
c. K Luck*, D-K Kim*, L Lambourne*, K Spirohn*, BE Begg, W Bian, R Brignall, T Cafarelli, FJ Campos-Laborie, B Charloteaux, D Choi, AG Cote,,, P Aloy, GD Bader, J De Las Rivas, S Gaudet, T Hao, J Rak, J Tavernier, V Tropepe, DE Hill†, M Vidal†, ***FP Roth***†, MA Calderwood†. A reference map of the human protein interactome. **Nature** 580(7803):402-408 (2020). [PMC7169983]

d. DK Kim*, B Weller*, CW Lin*, D Sheykhkarimli*, JJ Knapp*, G Dugied, A Zanzoni, C Pons, MJ Tofaute, SB Maseko, K Spirohn, F Laval, L Lambourne, N Kishore, A Rayhan,,, M Taipale, Y Jacob, T Hao, DE Hill, C Brun, JC Twizere, D Krapmann, M Heinig, C Falter, P Aloy, C Demeret†, M Vidal†, MA Calderwood†, ***FP Roth***†, P Falter-Braun†. A proteome-scale map of the SARS-CoV-2 human contactome. **Nature Biotechnology** 41(1):140-149 (2023). [PMC9849141]

5. Sequence analysis: I was an early contributor to the field of transcriptome data analysis, demonstrating that genome-scale expression data can be used to identify transcription factor binding motifs using AlignACE software. I also developed FuncAssociate, which was the first (before GSEA) and still widely used web-based software to detect functional enrichment in large-scale data sets. As microarray-based gene-clustering publications proliferated wildly, we developed a way to assess clustering methods based on their ability to group genes by function. Later, we explored a mysterious phenomenon relating absence of introns in 5' untranslated regions with mRNA export, with consequences for human proteins that are trafficked to the ER or mitochondrion. More recently, we've provided tools for more accurately sequencing collections of barcoded mutagenized clones (for use in variant effect mapping via Bar-Seq approaches).

a. ***FP Roth****, JD Hughes*, PW Estep & GM Church†. Finding DNA regulatory motifs within unaligned noncoding sequences clustered by whole-genome mRNA quantitation. **Nature Biotechnology**, 16: 939-945 (1998).

b. GF Berriz, OD King, B Bryant, C Sander & ***FP Roth***†. Characterizing gene sets with FuncAssociate. **Bioinformatics** 19(18):2502-2504 (2003).

c. C Cenik, HN Chua, G Singh, A Akef, MP Snyder, AF Palazzo, MJ Moore† & ***FP Roth***†. A common class of transcripts with 5'-intron depletion, distinct early coding sequence features, and N1-methyladenosine modification. **RNA.** 23(3):270-283 (2017). [PMC5311483]

d. J Weile, G Ferra,,, AG Cote, N Kishore, D Tabet, W van Loggerenberg, A Rayhan, DM Fowler, MJ Dunham, **FP Roth**†. Pacybara: Accurate long-read sequencing for barcoded mutagenized allelic libraries. **Bioinformatics** 40(4):btae182 (2024). [PMC11021806]

More complete publication list: https://scholar.google.com/citations?user=a2FJg9wAAAAJ