BIOGRAPHICAL SKETCH

NAME: Norbert Perrimon

eRA COMMONS USER NAME: PERRIMON

POSITION TITLE: James Stillman Professor of Developmental Biology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Paris VI, Paris, France	Maitrise	07/1981	Biochemistry
University of Paris VI, Paris, France	Ph.D.	06/1983	Developmental Genetics
Case Western Reserve University, Cleveland, OH	Postdoctoral	05/1986	Genetics

A. Personal Statement

I have more than 30 years of experience in the fields of developmental genetics, signal transduction and genomics. By developing, improving, and applying a number of genetic techniques (germline clones, FLP/FRT, Gal4/UAS, CRISPR, etc.), I identified many key components of the Receptor Tyrosine Kinases, JAK/STAT, Wnt, Hedgehog, and Notch signaling pathways. My group established high-throughput genome-wide RNAi screens and pooled CRISPR screens to systematically interrogate the entire *Drosophila* genome in various cell-based assays, and more recently extended CRISPR pooled screening to mosquito cells. In 2003, I created the *Drosophila* RNAi Screening Center (DRSC) at Harvard Medical School to make this technology available to the community. In addition, in 2008, I initiated the Transgenic RNAi Project (TRiP) to generate transgenic RNAi lines for the community using optimized shRNA vectors that my lab developed, and more recently transgenic gRNA lines for CRISPR loss of function and gain of function screens. Currently, my lab is applying large-scale RNAi and proteomic methods to obtain a global understanding to the structure of a number of signaling pathways and their crosstalk. In addition, I am studying the roles of signaling pathways in homeostasis and tissue remodeling in *Drosophila* muscles and gut stem cells, as well as hormonal systems involved in inter-organ communication. Since 2015, I have been the PI of the *Drosophila* database FlyBase. I have trained more than 120 students and postdoctoral fellows, most of whom currently hold academic positions. My lab is committed to creating and nourishing an environment that attracts diverse trainees and allows all members to thrive, grow, and excel.

B. Positions, Scientific Appointments, and Honors

2015 – Present Principal Investigator, FlyBase, Harvard University
2015 – Present Adjunct Professor, Molecular and Cellular Biology Department, Harvard University
2011 – Present James Stillman Professor of Developmental Biology, Harvard Medical School, Boston, MA
2006 – Present Associate Member, Broad Institute, Boston, MA
2005 – Present Member, Harvard Stem Cell Institute, Boston, MA
1997 – Present Investigator, Howard Hughes Medical Institute, Boston, MA
1996 – Present Professor, Harvard Medical School, Department of Genetics, Boston, MA
1993 – Present Associate Investigator, Howard Hughes Medical Institute, Boston, MA
1993 – Present Associate Professor, Harvard Medical School, Department of Genetics, Boston, MA
1986 – 1993 Assistant Investigator, Howard Hughes Medical Institute, Boston, MA
1986 – 1993 Assistant Professor, Harvard Medical School, Department of Genetics, Boston, MA
1983 – 1986 Postdoctoral Fellow, Dr. A. Mahowald Lab, Case Western Reserve University, Cleveland, OH

Honors

2018 Transformative Research Award, NIH
2013 Elected, National Academy of Sciences
2011 Elected, Associate Member of EMBO

2009	Elected, American Association for the Advancement of Science
2009	RNAi Innovator Award
2008	Elected, American Association of Arts and Sciences
2004	George W. Beadle Medal, Genetics Society of America
2003	Chaire d'Etat, College de France, Paris
1986 – Present	Howard Hughes Medical Institute Investigator Award
1985	Lucille P. Markey Scholar, Biomedical Sciences

C. Contributions to Science

1. Development of tools and methods for *in vivo* studies

Since the realization, half a century ago, that genes encode the building blocks of cells, identifying their functions has become a priority in the life sciences. Linking genotype to phenotype has been the most rewarding approach to identify the function of genes and over the years many advances in the field have been made possible by the development of methods that allow precise spatial and temporal control of gene activity. My lab has developed many methods that have significantly improved the *Drosophila* toolbox. These include: the GAL4-UAS method to control gene expression both spatially and temporally; the FLP-FRT Dominant Female Sterile technique to generate mosaics in the female germline that led to the characterization of the maternal effect of zygotic lethal mutations; thermosensitive inteins to generate conditional alleles; and the "Positively Marked Labeling Method" for lineage analyses that allows one to generate clones of mutant cells that express either GFP or LacZ. More recently, we have developed a number of tools based on CRISPR for genome engineering in flies.

a. Brand AH, **Perrimon N**. Targeted gene expression as a means of altering cell fates and generating dominant phenotypes. Development 1993 Jun;118(2):401-15. PMCID: N.A.
b. Chou TB, **Perrimon N**. The autosomal FLP-DFS technique for generating germline mosaics in *Drosophila melanogaster*. Genetics. 1996 Dec;144(4):1673-9. PMCID: PMC1207718.
c. Ewen-Campen B, Yang-Zhou D, Fernandes VR, González DP, Liu LP, Tao R, Ren X, Sun J, Hu Y, Zirin J, Mohr SE, Ni JQ, **Perrimon N**. Optimized strategy for *in vivo* Cas9-activation in *Drosophila*. Proc Natl Acad Sci U S A. 2017 Aug 29;114(35):9409-9414. PMCID: PMC5584449.
d. He L, Binari R, Huang J, Falo-Sanjuan J, **Perrimon N**. *In vivo* study of gene expression with an enhanced dual-color fluorescent transcriptional timer. Elife. 2019 May 29;8. pii: e46181. PMCID: PMC6660218.

2. Genome scale functional genomics approaches

The availability of the *Drosophila* genome sequence in 2000 provided an unprecedented resource for functional genomic studies. To address the issue that 75% of the genome is not yet functionally annotated, and to systematically analyze the functions of the ~14,000 predicted genes, we established a high-throughput screening platform to conduct RNA interference (RNAi) screens in *Drosophila* tissue culture cells in 384 well plates. We used this approach to perform many genome-wide RNAi screens mostly in cell signaling assays. We also demonstrated that long dsRNAs are associated with off target effects, established a cross-species method for rescue of RNAi phenotypes, developed RNAi methods in primary embryonic cell cultures, generated algorithms for automated image analyses, and used CRISPR to engineer cell lines for RNAi screens. In 2003, we established the *Drosophila* RNAi Screening Center to make this technology available to the community. To date the DRSC has supported more than 120 screens. In addition, we developed new shRNA vectors for *in vivo* RNAi and in 2008 established the Transgenic RNAi Project to build and validate a genome scale resource of transgenic shRNA flies. To date about 10,000 lines have been generated and are available from fly stock centers. More recently, we have established a platform for pooled CRISPR loss of function and gain of function screens that we are applying to perform screens for synthetic lethality and host pathogen interactions both in Drosophila and mosquito cells.

a. Boutros M, Kiger AA, Armknecht S, Kerr K, Hild M, Koch B, Haas SA, Heidelberg Fly Array Consortium, Paro R, **Perrimon N**. Genome-Wide RNAi Analysis of Growth and Viability in *Drosophila* Cells. Science 2004 Feb 6;303(5659):832-5. PMCID: N.A.
b. Ni JQ, Zhou R, Czech B, Liu LP, Holderbaum L, Yang-Zhou D, Shim HS, Tao R, Handler D, Karpowicz P, Binari R, Booker M, Brennecke J, Perkins LA, Hannon GJ, **Perrimon N**. A genome-scale shRNA resource for transgenic RNAi in *Drosophila*. Nat Methods. 2011 May;8(5):405-7. PMCID: PMC3489273.
c. Viswanatha R, Li Z, Hu Y, **Perrimon N**. Pooled genome-wide CRISPR screening for basal and context-

specific fitness gene essentiality in *Drosophila* cells. Elife. 2018 Jul 27;7. pii: e36333. PMCID: PMC6063728.

d. Viswanatha, R., Mameli, E., Rodiger, J., Merckaert, P., Feitosa-Suntheimer, F., Colpitts T, Mohr, S.E., Hu, Y. and **Perrimon, N.** (2021) Bioinformatic and cell-based tools for pooled CRISPR knockout screening in mosquitos. Nature Communications 12(1):6825. doi: 10.1038/s41467-021-27129-3. PMID: 34819517

3. Characterization of components of signaling pathways

Over the years, either from genetic screens *in vivo* or RNAi cell-based screens, we have characterized many components of conserved signaling pathways. Our early studies were instrumental in defining the canonical components of the receptor tyrosine kinases, Wnt, JAK/STAT, and JNK pathways. Major findings include: Raf kinase and demonstration that it acts downstream of Ras; Corkscrew/SHP2 non receptor tyrosine phosphatase as a positive transducer of RTK signaling; Spitz as a ligand, and Kekkon as a negative regulator of EGFR; Porcupine, Dishevelled and GSK3 as components of Wnt/Wg signaling; Unpaired, Hopscotch/JAK and Marelle/STAT as members of the JAK/STAT pathway; Heparan Sulfate Proteglycans in Hedgehog, Wnt and FGF signaling; and the identification of Scribble and the organization of the cell polarity complexes. Using large-scale proteomics and RNAi screens our lab generated comprehensive networks of the MAPK, AKT, and Hippo pathways.

a. Bilder D, Li M, **Perrimon N**. Cooperative regulation of cell polarity and growth by *Drosophila* tumor suppressors. Science. 2000 Jul 7;289(5476):113-6. PMCID: N.A

b. Bakal C, Linding R, Llense F, Heffern E, Martin-Blanco E, Pawson T, **Perrimon N**. Phosphorylation Networks Regulating JNK Activity in Diverse Genetic Backgrounds. Science. 2008 Oct 17;322(5900):453-6. PMCID: PMC2581798.

c. Kwon Y, Arunachalam V, Sun X, Dephoure N, Gygi SP, Hong P, **Perrimon N**. The Hippo signaling pathway interactome. Science. 2013 Nov 8;342(6159):737-40. PMCID: PMC3951131.

d. Tang HW, Hu Y, Chen CL, Xia B, Zirin J, Yuan M, Asara JM, Rabinow L, **Perrimon N**. The TORC1-Regulated CPA Complex Rewires an RNA Processing Network to Drive Autophagy and Metabolic Reprogramming. Cell Metab. 2018 Mar 16. pii: S1550-4131(18)30134-7. PMCID: PMC6100782.

4. Signaling mechanisms involved in gut regeneration

Under normal tissue homeostasis, committed stem cells slowly divide to replace differentiated cells. When many cells are lost due to injury, they are replaced expediently by an increase in the rate of stem cell division. As new cells are produced, the damaged tissue is regenerated, eventually returning to its correct size and to normal homeostasis. A few years ago, we discovered that homeostasis in the adult gut depends on proper proliferation and differentiation of stem cells (Intestinal Stem Cells or ISCs). Subsequently, our group and others have used this system to dissect the signaling pathways involved in gut homeostasis providing a detailed understanding of the intricate cross-talk between RTKs, Wnt, Hh, TGFb, Insulin, JNK, JAK/STAT pathways in a stem cell system, and how their activities are regulated by circadian activity, diet, aging and hormones.

a. Micchelli C, **Perrimon N**. Evidence that stem cells reside in the adult *Drosophila* midgut epithelium. Nature. 2006 Jan 26;439(7075):475-9. Epub 2005 Dec 7. PMCID: N.A.

b. Kim K, Hung RJ, **Perrimon N**. miR-263a regulates ENaC to maintain osmotic and intestinal stem cell homeostasis in *Drosophila*. Dev Cell. 2017 Jan 9;40(1):23-36. PMCID: PMC5224988.

c. He L, Si G, Huang J, Samuel ADT, **Perrimon N**. Mechanical regulation of stem-cell differentiation by the stretch-activated Piezo channel. Nature. 2018 Mar 1;555(7694):103-106. PMCID: PMC6101000.

d. Xu, C., Xu, J., Tang, H-W., Ericsson, M., Weng, J-H., DiRusso, J., Hu, Y., Ma, W., Asara, J. M. and **Perrimon, N.** (2023) A phosphate-sensing organelle regulates phosphate and tissue homeostasis. Nature. doi: 10.1038/s41586-023-06039-y. PMID: 37138087

5. Communication between organs

Organ-to-organ communications are critical to living systems and play major roles in homeostasis. For example, the vertebrate CNS receives information regarding the status of peripheral metabolic processes via hormonal signaling and direct macromolecular sensing. In addition, skeletal muscles produce various myokines that influence metabolic homeostasis, lifespan, and the progression of age-related diseases and aging in non-muscle tissues. *Drosophila* is a prime system for systematically identifying mechanisms involved in organ communication because libraries of transgenic RNAi lines are available that allow knockdown of any gene in an organ or tissue-specific manner. From such, genetic screens we have already characterized a number of secreted factors (ImpL2/IBP; Myostatin/GDF11; Upd/Leptin; Activin-beta; Pvf1/PDGF) by which

organs communicate their physiological state to others. These genetic screens are combined with RNAseq of specific organs to define the transcriptional signatures corresponding to their homeostatic states, and Mass Spec analyses from blood to characterize secreted factors. These studies are providing fundamental insights into how biological processes observed in one tissue/organ (e.g., decreased cellular metabolism, mitochondrial dysfunction) influence the state of other tissues/organs. These studies are relevant to metabolic disorders and aging in particular.

a. Rajan A, **Perrimon N**. *Drosophila* cytokine Unpaired 2 regulates physiological homeostasis by remotely controlling Insulin secretion. Cell. 2012 Sep 28;151(1):123-37. PMCID: PMC3475207.
b. Owusu-Ansah E, Song W, **Perrimon N**. Muscle mitohormesis promotes longevity via systemic repression of Insulin signaling. Cell. 2013 Oct 24;155(3):699-712. PMCID: PMC3856681.
c. Song W, Cheng D, Hong S, Sappe B, Hu Y, Wei N, Zhu C, O'Connor MB, Pissios P, **Perrimon N**. Midgut-Derived Activin Regulates Glucagon-like Action in the Fat Body and Glycemic Control. Cell Metab. 2017 Feb 7;25(2):386-399. PMCID: PMC5373560.
d. Song W, Kir S, Hong S, Hu Y, Wang X, Binari R, Tang HW, Chung V, Banks AS, Spiegelman B, **Perrimon N**. Tumor-Derived Ligands Trigger Tumor Growth and Host Wasting via Differential MEK Activation. Dev Cell. 2019 Jan 28;48(2):277-286.e6. PMCID: PMC636835.

Complete List of Published Work:

https://pubmed.ncbi.nlm.nih.gov/?term=perrimon&sort=date