BIOGRAPHICAL SKETCH

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NAME: Norbert Perrimon

eRA COMMONS USER NAME (credential, e.g., agency login): PERRIMON

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Paris VI	Maitrise	07/1981	Biochemistry
University of Paris VI	Ph.D.	06/1983	Developmental Genetics

A. Personal Statement

Dr. Perrimon has 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.), his group identified many key components of the Receptor Tyrosine Kinases, JAK/STAT, Wnt, Hedgehog, and Notch signaling pathways. His group established high-throughput genome-wide RNAi screens and pooled CRISPR screens to systematically interrogate the entire *Drosophila* genome in various cell-based assays. In 2003, he created the *Drosophila* RNAi Screening Center at Harvard Medical School to make this technology available to the community. In addition, in 2008, he initiated the Transgenic RNAi Project to generate transgenic RNAi lines for the community using optimized shRNA vectors that his lab developed, and more recently transgenic gRNA lines for CRISPR loss of function and gain of function screens. Currently, his 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 cross-talks. In addition, he is 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, he has been the PI of the *Drosophila* database FlyBase. Dr. Perrimon has trained more than 100 students and postdoctoral fellows, most of whom currently hold academic positions.

B. Positions and Honors

Positions

1983-1986 *Postdoctoral Fellow* – Dr. A.P. Mahowald Lab, Case Western Reserve University, Cleveland, OH
1986-1993 *Assistant Professor* – Harvard Medical School, Department of Genetics, Boston, MA
1986-1993 *Assistant Investigator* – Howard Hughes Medical Institute, Boston, MA
1993-Date *Associate Professor* – Harvard Medical School, Department of Genetics, Boston, MA
1993-Date *Associate Investigator* – Howard Hughes Medical Institute, Boston, MA
1996-Date *Professor* – Harvard Medical School, Department of Genetics, Boston, MA
1997-Date *Investigator* – Howard Hughes Medical Institute, Boston, MA
2005-Date *Member* – Harvard Stem Cell Institute, Boston, MA
2006-Date *Associate Member* – Broad Institute, Boston, MA
2011-Date *James Stillman Professor of Developmental Biology* – Harvard Medical School, Boston, MA

Awards and Honors

1985 Lucille P. Markey Scholar – Biomedical Sciences
1986-Date Investigator – Howard Hughes Medical Institute
2003 Chaire d'Etat – College de France, Paris
2004 George W. Beadle Medal – Genetics Society of America

2008 Elected – American Association of Arts and Sciences
2009 RNAi Innovator Award
2009 Elected – American Association for the Advancement of Science
2011 Elected – Associate Member of EMBO
2013 Elected – National Academy of Sciences
2018 Transformative Research Award, NIH

Distinguished Lectures / Keynotes (past 5 years)
Keynotes: Northwest Developmental Meeting (2014). RNAi/CRISPR Meeting (2014). Model Organism Resources (2014). NTU opening symposium (2015). Trans-NIH Developmental Biology Group, National Institutes of Health (2015). 45th Annual Meeting, Brazilian Society of Biochemistry and Molecular Biology, Natal, Brazil (2016). USIAS Public Lecture, Strasbourg, France (2017). Societe Francaise de Genetique, Montpellier, France (2017). ERATO / CREST / PREST Joint International Symposium "Inter-Organ Communication, Kyoto, Japan (2017). Annual Kaulenas Lecture, University of Massachusetts-Amherst (2015). USIAS Public Lecture, Strasbourg (2017).

Panels, Committees, Scientific Advisory Boards (past 5 years): U.S. *Drosophila* Stock Center Advisory Board (1996-). IGBMC, Strasbourg – Scientific Advisory Board (2006-). ERC Horizon 2020 (2015-2020). Venitian Institute of Molecular Medicine – Scientific Advisory Board (2016-). Alliance for Genomics Research (AGR) Scientific Advisory Board (2016-). TATA Institute of Genetics and Society – Scientific Advisory Board (2018-).

Editorial Boards (Current): BioMed Central Dev. Biol. (2000-). Molecular and Cellular Biology (2000-). Faculty of 1000 (2001-). International Journal of Developmental Biology (2002-). Genome Biology (2008-). PLoS Genetics (2008-). Science Signaling, (2008-) Genetics (2008-). Developmental Cell (2009-). Molecular Systems Biology (2009-). WIRES-Developmental Biology (2010-). EMBO Reports (2011-). Flybook (2015-). Diseases, Models and Mechanisms (2016-). BioMed Central-Biology (2016-).

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: *In Process*.

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 (DRSC; http://flyrnai.org) 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 (TRiP; http://www.flyrnai.org/TRiP-HOME.html) 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.

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. Bakal C, Aach J, Church G, **Perrimon N**. Quantitative morphological signatures define local signaling networks regulating cell morphology. Science 2007 Jun 22;316(5832):1753-6. PMCID: N.A.
c. 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.
d. 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.

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. Song W, Veenstra JA, **Perrimon N**. Control of lipid metabolism by Tachykinin hormones. Cell Rep. 2014 Oct 9;9(1):40-7. PMCID: PMC4325997.
c. 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.
d. 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.

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/IGFBP; Myostatin/GDF11; Upd2/Leptin; Activin-beta) 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 in MyBibliography

http://www.ncbi.nlm.nih.gov/sites/myncbi/norbert.perrimon.1/bibliograpahy/40332307/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support – Perrimon Lab

Grant # N.A. Perrimon 09/01/2018–08/31/2019
Howard Hughes Medical Institute – "Pattern formation in *Drosophila*"
The major goals of this project are the studies of *Drosophila* signal transduction pathways and cell polarity in patterning the *Drosophila* embryo and imaginal discs.

R01AR057352 Perrimon 05/01/2010–04/30/2020
NIH/NIAMS – "Characterization of the Insulin to Autophagy Pathway in Muscles"
These studies will address the role of Insulin and FOXO in regulating anabolic and catabolic pathways during muscle growth and aging in *Drosophila*. Because of the evolutionary conservation of Insulin signaling and the basic cellular machinery involved in protein degradation, our findings in the *Drosophila* model will be directly relevant to the understanding of muscle wasting associated with muscular dystrophies, cachexia and sarcopenia.

P01CA120964 Kwiatkowski/Perrimon & Manning sub 07/01/2018–06/30/2023
Brigham & Women's Hospital (NIH/NCI) – "Molecular Pathogenesis of the Hamartoma Syndromes: Project 1 – Molecular wiring and therapeutic targeting of the TSC-Rheb signaling network"
The major goal of this project is to use a dsRNA mini-library containing all kinases and phosphatases encoded

in the *Drosophila* genome to search for components regulating AMPK activity. There is no overlap with the R01AR057352 competitive renewal.

Ongoing Research Support–DRSC/TRiP (support for the *Drosophila* community, not the Perrimon laboratory)

P41GM132087 Perrimon 08/01/2019 – 03/31/2024
NIH/NIGMS – "Functional genomics resources for the *Drosophila* and broader research communities"
This project is to renew ongoing support for the *Drosophila* RNAi Screening Center which provides RNAi and gRNA cell-based reagents to the community.

R01GM084947 Perrimon 09/01/2016–07/31/2020
NIH/NIGMS – "*Drosophila* Transgenic RNAi Resource Project"
Dr. Perrimon is the PI on this grant that supports funding for the *Drosophila* Transgenic RNAi Project at Harvard Medical School.

R01DK121409 Perrimon, Sub: Carr, McMahon, Ting 09/25/2018–06/30/2023
NIH/OD – "Mapping protein communication between organs in homeostasis and disease"
This project is to develop the BirA labeling system to identify secreted factors in the mouse. The Perrimon lab will provide its expertise with the use of these reagents. There is no overlap with Aim 3.2 of the R01AR057352 competitive renewal.