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, etc.), his group identified many key components of the Receptor Tyrosine Kinases, JAK/STAT, Wnt, Hedgehog and Notch signaling pathways. In recent years, his group established high-throughput genome-wide RNAi 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. Currently, his laboratory 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. Dr. Perrimon has trained more than 90 students and postdoctoral fellows, most of whom currently hold academic positions.

B. Positions and Honors

Positions

1983-1986 *Postdoctoral Research 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

Distinguished Lectures / Keynotes (past 10 years)

Keynotes: Lorne Cancer Conference (2008). Protein Phosphorylation, Salk (2008). Sheffield Symposium (2008). RNAi Summit (2009). ICDB Retreat, Star Institute Singapore (2009). Recomb 2010. Asian *Drosophila* Meeting (2011). Montreal Bioinformatics User Group (2011). 25th French *Drosophila* Conference (2011). Integrative Network Biology (2012). From Stem Cells to Morphogenesis, Curie Institute (2012). Keynote: UK Genes & Cancer Meeting (2012). ICSB (2013). FEBS JAK/STAT Signaling (2013). 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).

Distinguished Lectures: Distinguished Lecturer, Fox Chase (2008). Distinguished Lecturer, National Cancer Institute (2008). Society of Fellows, Scripps (2009). Alma Howard Lecture, McGill University (2011). Blaffer Lecture, MD Anderson (2011). Sarah Winans Newman Lecture, University of Michigan (2012). Annual Kaulenas Lecture, University of Massachusetts-Amherst (2015).

Panels, Committees, Scientific Advisory Boards (past 10 years)

Past: NSF SBIR Panel (2007). Harvard Medical School Scientific Advisory Committee on siRNA Technology (2007-2010). GATC NIH Study Section (2008). ERC Reviewer (2008-2009). Labex Committee (2011). Charles A. King Trust Postdoctoral Research Fellowship Program (2012-2015). Max Planck Institute for Biology of Aging, Cologne – Scientific Advisory Board, (2011-2016). HFSP Writing Group on Life Science and Biomedical Databases (2016).

Current: 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-).

Editorial Boards (past 10 years)

Past: Editorial Board, *Developmental Biology* (1995-2007). Review Editor, *Developmental Cell* (2001-2008). Editorial Board, *Mechanisms of Develop*ment (1999-2010). Advisor, *Nature Reviews in Molecular and Cell Biology* (2000-2011). Co-Editor with Dr. N. Barkai, *Current Opinion in Genetics and Development* (2011).

Current: Editorial Board, *BioMed Central Dev. Biol.* (2000-). Editorial Board, *Molecular and Cellular Biology* (2000-). Associate, Faculty of 1000 (2001-). Editorial Board, *International Journal of Developmental Biology* (2002-). Editorial Board, *BioMed Central Genomics* (2005-). Editorial Board, *Genome Biology* (2008-). Associate Editor, *PLoS Genetics* (2008-). Editorial Board, *Science Signaling,* (2008-) Associate Editor, *Genetics* (2008-). Editorial Board, *BioMed Central Silence* (2009-). Editorial Board, *Developmental Cell* (2009-). Associate Editor, *Molecular Systems Biology* (2009-). Associate Editor, *WIRES-Developmental Biology* (2010-). Associate Editor, *EMBO Reports* (2011-). Advisory Board, *Development* (2013-). Editorial Board, *Flybook* (2015-). Editorial Board, *Diseases, Models and Mechanisms* (2016-). Editorial Board, *BioMed Central-Biology* (2016-).

C. Contribution 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. Over the years, my group 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. Zeidler M, Tan C, Bellaiche Y, Cherry S, Häder S, Gayko U, **Perrimon N**. Temperature-sensitive control of protein activity by conditionally splicing inteins. Nature Biotechnol. 2004 Jul;22(7);871-6. PMCID: N.A.

d. Griffin R, Sustar A, Bonvin M, Binari R, del Valle Rodriguez A, Hohl AM, Bateman J, Villalta C, Heffern E, Grunwald D, Bakal C, Desplan C, Schubiger G, Wu CT, **Perrimon N**. The Twin Spot Generator for differential *Drosophila* lineage analysis. Nat Methods. 2009 Aug;6(8):600-2. PMCID: PMC2720837.

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. Housden BE, Valvezan AJ, Kelleym C, Sopko R, Hu Y, Roese C, Lin S, Buckner M, Tao R, Yilmazel B, Mohr S, Manning B, **Perrimon N**. Identification of novel drug targets for Tuberous Sclerosis Complex by synthetic screens combining CRISPR-based knockouts with RNAi. Sci Signal. 2015 Sep 8;8(393):rs9. PMCID: PMC4642709.

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. Siegfried E, Chou TB, **Perrimon N**. *wingless* signaling acts through *zeste-white 3*, the *Drosophila* homologue of g*lycogen synthase kinase-3*, to regulate *engrailed* and establish cell fate. Cell. 1992 Dec 24;71(7):1167-79. PMCID: N.A.

b. 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

c. 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.

d. Kwon Y, Arunachalam V, Sun X, Dephoure N, Gygi SP, Hong P, **Perrimon N**. The Hippo signaling pathway interactome. Science. 013 Nov 8;342(6159):737-40. PMCID: PMC3951131.

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. Karpowicz P, Zhang Y, Hogenesh JB, Emery P, **Perrimon N**. The circadian clock gates the intestinal stem cell regenerative state. Cell Rep. 2013 Apr 25;3(4):996-1004. PMCID: PMC3982394.

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

d. 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.

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. Kwon Y, Song W, Droujinine I, Hu Y, Asara JM, **Perrimon N**. Systemic organ wasting induced by localized expression of the secreted Insulin/IGF antagonist ImpL2. Dev Cell. 2015 Apr 6;33(1):36-46. PMCID: PMC4437243.

d. 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.

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 09/01/2017–08/31/2018
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.

Ongoing Research Support–DRSC/TRiP These grants support the *Drosophila* community and not the Perrimon laboratory. There is no overlap between these funding sources and the submitted proposal.

R01GM067761 Perrimon 05/01/2011–11/30/2020
NIH/NIGMS – "Functional Genomics Analysis Using RNAi Screen in *Drosophila*"
Dr. Perrimon is the PI on this grant that supports funding for the *Drosophila* RNAi Screening Center at Harvard Medical School.

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.

R01HG007118 Perrimon (PI), Celniker, Vidal (Co-PIs) 09/01/2012–06/30/2018
NIH/NHGRI – "Large-Scale High-Confidence Binary Protein Interaction Network for *Drosophila*"
The major goal of this project is to perform a state-of-the-art, high-throughput, quality-controlled analysis of binary protein interactions in *Drosophila*. The resulting next-generation "interactome" will provide a much more complete picture of possible protein interactions in this model system.