BIOGRAPHICAL SKETCH

NAME: Norbert Perrimon

POSITION TITLE: Professor

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

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 crosstalks. 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 80 students and postdoctoral fellows, with most of them currently holding academic positions.

**B. Positions and Honors**

**Professional Experience**

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| --- | --- |
| 1983-1986 | Postdoctoral Research Fellow with Dr. A.P. Mahowald at Case Western Reserve University |
| 1986-1993 | Assistant Professor, Department of Genetics, Harvard Medical School  Assistant Investigator, Howard Hughes Medical Institute |
| 1993-present | Associate Professor, Department of Genetics, Harvard Medical School  Associate Investigator, Howard Hughes Medical Institute |
| 1996-present | Professor, Department of Genetics, Harvard Medical School |
| 1997-present  2005-present | Investigator, Howard Hughes Medical Institute  Harvard Stem Cell Institute, Member |
| 2006-present  2011-present | Associate Member Broad Institute  James Stillman Professor of Developmental Biology |

**Awards**

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| --- | --- |
| 1985 | Lucille P. Markey Scholar in Biomedical Sciences |
| 1986-present | 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  2011  2013 | Elected, American Association for the Advancement of Science  Elected, Associate Member of EMBO  Elected, National Academy of Sciences |

**Distinguished Lectures**

Keynote: FASEB meeting. Protein Phosphatases, 1994. Keynote: Developmental Biology meeting, 1994. Keynote: French Developmental Biology meeting, Marseille, 2001. Keynote: Ohio University, 2001.Keynote: Japanese Cell Biology meeting, Yokohama, 2002. Boehringer Ingelheim Lecture, IRCM Montreal, 2002. Keynote: Bone and Teeth GRC, 2003. Sloan Kettering, President Lecture, 2003. R. Williams Lecture (Penn), 2004. Richard Akeson Lecture (Cincinnati), 2004. UCSD, Distinguished Lecturer, 2004. Keynote: FASEB meeting on Growth Factor signaling, 2005. Keynote: Keystone meeting on Signaling Networks, 2006. Sterling Lecture, DFCI, 2006. Fox Chase, Distinguished Lecturer, 2008. NCI, Distinguished Lecturer, 2008. Keynote: Lorne Cancer conference, 2008. Keynote: Protein Phosphorylation, Salk, 2008. Keynote: Sheffield Symposium, 2008. Keynote: RNAi Summit Boston, 2009. Society of Fellows, Scripps 2009. Keynote: ICDB retreat, Star Institute Singapore, 2009. Keynote: Recomb 2010, Lisbon. Alma Howard Lecture, McGill, 2011. Keynote: Asian *Drosophila* meeting, Taiwan, 2011. Keynote: Montreal Bioinformatics User Group, 2011. Blaffer lecture MD Anderson, 2011. Keynote: 25th French *Drosophila* Conference, 2011. Sarah Winans Newman lecture, Ann Harbor, 2012. Keynote: Integrative Network Biology 2012, Denmark. Keynote: From stem cells to morphogenesis, Curie Institute, 2012. Keynote: UK Genes & Cancer meeting 2012. Keynote: ICSB, Coppenhagen, 2013. Keynote, FEBS JAK/STAT signaling, Nottingham, 2013. Keynote: 2014 Northwest Developmental Meeting. Keynote: 2014 RNAi/CRISPR meting, San Diego. Keynote: 2014 Model Organism Resources. Keynote: 2015 NTU opening symposium, Singapore. 2015: Annual Kaulenas Lecture. Keynote: 2015 Trans-NIH Developmental Biology Group, NIH.

**Panels, Committees, Scientific Advisory Boards**

*Past:* NSF.Review Panel. Biological Instrumentation and Resources, 1991-1992.NSF, Academic Research Infrastructure, 1992. NCI, NIH. Member Special Study Section, 1994 -1995.NINDS, NIH. AdHoc reviewer, 1997.NSF, Developmental Mechanisms Review Panel, 1993-1998. CNRS, Marseille, Scientific Review Committee, 1999. Drosophila Developmental Biology Crete meeting committee, 1995-2008. CNRS review committee, Curie UMR-144, 2002. EMBL, Scientific Review Committee, 2003. MDCN-5, NIH. Study Section, 2003. HFSP Fellowship review committee, 2004-2007. ZRG1 FO5 NIH Fellowships Study Section, 2004-2006.Carnegie Institute, Scientific Review Committee, 2004. MGB, NIH. Study Section, 2005. Cell Biology Keystone Symposia Study Group, 2005. Scientific Review Group ZNS1 SRB, 2006. ZRG1 FO5 NIH Fellowships Study Section, 2004-2006. 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.

*Current:* U.S. Drosophila Stock Center Advisory Board, 1996-present. IGBMC, Strasbourg - Scientific Advisory Board, 2006-present. Max Planck Institute for Biology of Aging (Cologne) - Scientific Advisory Board, 2011-2016. Charles A. King Trust Postdoctoral Research Fellowship Program. 2012-2015. Flybase PI 2015.

**Editorial Boards**

*Past:* Guest Editor. Issue of Methods on Manipulation of gene expression, 1998. Co-Editor with Dr. C. Stern, Current Opinion in Cell Biology, 1999. Co-Editor with Dr. M. Bernfield, Seminars in Cell Biology, 2001. Principle Editor, Signaling. TheScientificWorld, 2000-2002. Genes and Development, Editorial Board, 1999-2004. Advisor for Nature Cell Biology, 2001-2002. Development, Editorial Board, 1999-2006. Developmental Biology, Editorial Board, 1995-2007. Review Editor, Developmental Cell, 2001-2008. Mechanisms of Development, Editorial Board, 1999-2010. Advisor for Nature Reviews in Molecular and Cell Biology, 2000-2011. Co-Editor with Dr. N. Barkai, Current Opinion in Genetics and Development, 2011.

*Current:* BioMed Central Dev. Biol., Editorial Board, 2000-present. Molecular and Cellular Biology, Editorial Board, 2000-present. Associate of Faculty of 1000, 2001-present. The International Journal of Developmental Biology, Editorial Board, 2002-present. BioMed Central Genomics, Editorial Board, 2005-present. Genome Biology, 2008-present. PLoS Genetics, Associate Editor 2008-present. Science Signaling, Editorial Board, 2008-present. Genetics, Associate Editor 2008-present. BioMed Central Silence, Editorial Board, 2009-present. Editorial Board Developmental Cell, 2009-present. Molecular Systems Biology, Associate Editor, 2009-present. WIRES-Developmental Biology, Associate Editor, 2010-present. EMBO Reports, Associate Editor, 2011-present.

**C. Most significant contributions to science**

A complete list of Dr. Perrimon’s publications can be found at: http://perrimon.med.harvard.edu/ResearchPapers.html

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

**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.

Brand, A. and Perrimon, N. (1993) Targeted gene expression as a means of altering cell fates and generating dominant phenotypes. Development **118**, 401-415. PMID: 8223268.

Chou, T.-B. and Perrimon, N. (1996). The autosomal FLP-DFS technique for generating germline mosaics in *Drosophila melanogaster*. Genetics **144**, 1673-1679. PMID: 8978054. PMCID: PMC1207718.

Zeidler, M., Tan, C., Bellaiche, Y., Cherry, S., Häder, S., Gayko, U. and Perrimon, N. (2004) Temperature-sensitive control of protein activity by conditionally splicing inteins. Nature Biotechnology **22**. 871-879. PMID: 15184905.

Griffin, R., Sustar, A., Bonvin, M., Binari, R., del Valle Rodriguez, A., Hohl, A. M., Bateman, J., Villalta, C., Heffern, E., Grunwald, D., Bakal, C., Desplan, C., Schubiger, G., Wu, C. T. and Perrimon, N. (2009) The Twin Spot Generator for differential *Drosophila* lineage analysis. Nature Methods. **6**, 600-602. PMID: 19633664. PMCID: PMC2720837.

**2. Genome scale functional genomics approaches.** The availability of the *Drosophila* genome sequence in year 2000 has provided us with 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. Todate 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.

Boutros, M., Kiger, A. A., Armknecht, S., Kerr, K. Hild, M., Koch, B., Haas, S. A., Heidelberg Fly Array Consortium., Paro, R., and Perrimon, N. (2004) Genome-Wide RNAi Analysis of Growth and Viability in *Drosophila* Cells. Science **303**. 832-835. PMID: 14764878.

Bakal, C., Aach, J., Church, G. and Perrimon, N. (2007) Quantitative morphological signatures define local signaling networks regulating cell morphology. Science **316,** 1753-1756. PMID: 17588932.

Ni, J-Q., Zhou, R., Czech, B., Liu, L-P., Holderbaum, L., Yang-Zhou, D., Shim, H-S., Tao, R., Handler, D., Karpowicz, P., Binari, R., Booker, M., Brennecke, J., Perkins, L. A. Hannon, G. J. and Perrimon, N. (2011) A genome-scale shRNA resource for transgenic RNAi in *Drosophila*. Nature Methods **8**, 405-7. PMID: 21460824. PMCID: PMC3489273.

Housden, B. E., Valvezan, A., J., Kelleym, C., Sopko, R., Hu, Y., Roese, C., Lin, S., Buckner, M., Tao, R., Yilmazel, B., Mohr, S., Manning, B., and Perrimon, N. (2015) Identification of novel drug targets for Tuberous Sclerosis Complex by synthetic screens combining CRISPR-based knockouts with RNAi. Science Signaling. Science Signaling 8:rs9. PMID: 26350902. 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.

Siegfried, E. Chou, T-B, and Perrimon, N. (1992) *wingless* signaling acts through *zeste-white 3*, the *Drosophila* homologue of g*lycogen synthase kinase-3*, to regulate *engrailed* and establish cell fate. Cell **71**, 1167-1179. PMID: 1335365.

Bilder, D., Li, M. and Perrimon, N. (2000) Cooperative regulation of cell polarity and growth by *Drosophila* tumor suppressors. Science **289**, 113-116. PMID: 10884224.

Bakal, C.,Linding, R., Llense, F., Heffern, E., Martin-Blanco, E.,Pawson, T. andPerrimon, N. 28 Phosphorylation Networks Regulating JNK Activity in Diverse Genetic Backgrounds. Science. **322**, 453-456. PMID: 18927396. PMCID: PMC2581798.

Kwon, Y., Arunachalam, V., Sun, X., Dephoure, N., Gygi, S. P., Hong, P. and Perrimon, N. (2013)The Hippo signaling pathway interactome. Science. **342**, 737-40. PMID: 24114784. 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.

Micchelli, C. and Perrimon, N. (2006) Evidence that stem cells reside in the adult *Drosophila* midgut epithelium. Nature. **439**, 475-479. PMID: 16340959.

Karpowicz, P., Perez, J. and Perrimon, N. (2010) The Hippo tumor suppressor pathway regulates intestinal stem cell regeneration. Development. **137**, 4135-4145. PMID: 21098564. PMCID: PMC2990205.

Karpowicz, P., Zhang, Y., Hogenesh, J. B., Emery, P. and Perrimon, N. (2013) The circadian clock gates the intestinal stem cell regenerative state. Cell Reports. **3**, 996-1004. PMID: 23583176. PMCID: PMC3982394.

Song, W., Veenstra, J. A. and Perrimon, N. (2014) Control of lipid metabolism by Tachykinin hormones. Cell Reports. **9**: 40-47. PMID:25263556. PMCID: PMC4325997.

**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.

Demontis, F. and Perrimon, N. (2010) FOXO/4E-BP signaling in *Drosophila* muscles regulates organism-wide proteostasis during aging. Cell. **143**, 813-825. PMID: 21111239. PMCID: PMC3066043.

Rajan, A. and Perrimon, N. (2012) *Drosophila* cytokine Unpaired 2 regulates physiological homeostasis by remotely controlling Insulin secretion. Cell. **151**, 123-137. PMID: 23021220. PMCID: PMC3475207.

Owusu-Ansah, E., Song, W. and Perrimon, N. (2013) Muscle mitohormesis promotes longevity via systemic repression of Insulin signaling. Cell. **155**, 699-712. PMID: 24243023. PMCID: PMC3856681.

Kwon, Y., Song, W., Droujinine, I., Hu, Y., Asara, J. M. and Perrimon, N. (2015) Systemic organ wasting induced by localized expression of the secreted Insulin/IGF antagonist ImpL2. Developmental Cell. **33**:36-46. PMID:25850671. PMCID: PMC4437243.