PROFILE

Profile of Norbert Perrimon

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As a child, one of Norbert Perrimon's first introductions to the scientific method came from his father. Perrimon's father was interested in geology. "Often we would go to various areas in Normandy, where I grew up, and collect different types of soils, rocks, and fossils. I always found it quite interesting to see how from the collection of different bits and pieces, you could draw complex geological maps," Perrimon says. Many years later, Perrimon would use a similar process to make his mark not in geology, but as a biologist working on the fruit fly, *Drosophila*.

Over a long and distinguished career, Perrimon combined different pieces of data collected from the study of various fruit fly mutants to map complex developmental and signaling pathways. In recognition of his discoveries in the field of *Drosophila* development and signaling, and for developing important genetic tools for studying fruit flies, Perrimon was elected to the National Academy of Sciences in 2013. Now a professor of developmental biology and genetics at Harvard Medical School, Perrimon first started developing tools to study fruit fly genetics as a graduate student at the University of Paris.

Creating Mosaics

It was in the early 1980s that Perrimon first became interested in genetics as a tool to tackle questions in developmental biology and embryology. "I was looking for an organism where I could use genetics to study the complexity of the way animals form," he says. "I started working in *Drosophila* because it is a great model system to apply genetics." In 1981, he started his doctoral research studying fruit fly oogenesis in the laboratory of Madeleine Gans at the University of Paris.

At the time, researchers were beginning to use fruit flies to identify genes involved in early development. "This was an exciting time because a number of important findings regarding patterning and the way animals develop had just been made," Perrimon says. In particular, genetic screens conducted by developmental biologists Christiane Nüsslein-Volhard and Eric F. Wieschaus had shown that a single mutation could have specific effects on the development of the embryo (1). "It became quite clear that some genes could control developmental decisions, suggesting that characterization of these genes would lead to a molecular understanding of patterning. This was the kind of science I wanted to do," Perrimon says.

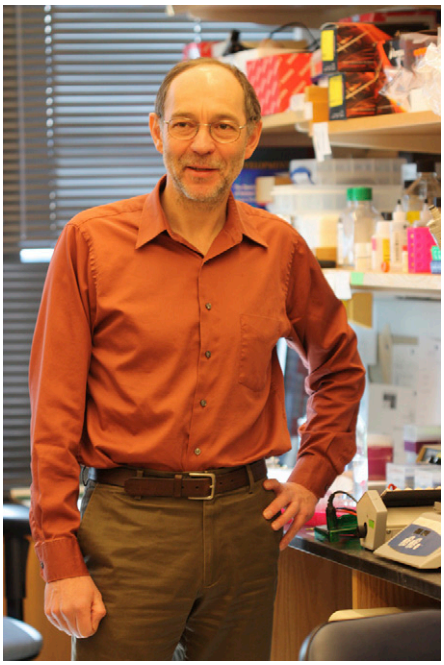
During his doctoral work, which he completed with Anthony Mahowald at Case Western Reserve University in Cleveland, Perrimon became interested in developing ways to isolate and characterize mutations that affected embryonic development. He developed a technique, called the "dominant female sterile method," to study the maternal effect of mutations in genes that are essential for flies (2). "You can't look at embryos derived from females that are homozygous mutant for a gene that is essential for viability because those flies are dead, so you need to create mosaics," Perrimon says. Mosaic organisms contain cells with two or more different genotypes, and the dominant female sterile method allows researchers to produce female flies that do not express an essential gene product during oogenesis, Perrimon says. "So we were able to look at embryos, which were derived from eggs that were completely depleted for an essential gene."

Developing the dominant female sterile technique to identify genes involved in fly development comprised the bulk of Perrimon's thesis work. "This mosaic technique allowed us to identify many new genes, which have very specific effects in early embryonic development," Perrimon says. After he started his own laboratory at Harvard Medical School in 1986, Perrimon would go on to develop other techniques to create mosaics, including one that had a particularly large impact on the fruit fly field.

Influential Technique

In his Inaugural Article, Perrimon reviews different methods that he and his colleagues have generated over the years for creating mosaics (3).

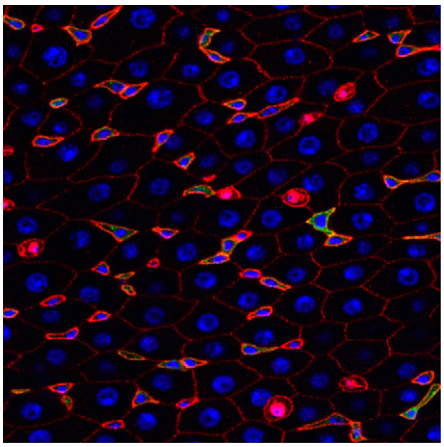
One of the key techniques Perrimon developed, together with Gurdon Institute molecular biologist Andrea Brand, is the Gal4-UAS system to control gene expression in a spatial and temporal way (4). The system consists of the yeast *GAL4* gene, which encodes the transcriptional activator Gal4, and a stretch of DNA called the Upstream Activation Sequence (UAS), an enhancer to which Gal4 specifically binds to activate transcription. "It allowed us to control where and when we could express a specific gene," Perrimon says. "This has very broad applications throughout the field in terms of allowing conditional tissue-specific gene expression."



Norbert Perrimon. Photo courtesy of Norbert Perrimon.

Perrimon developed the Gal4-UAS system because he wanted to express the activated form of kinases that were important for fly development, he says. "Activated kinases, if you express them ubiquitously in the fly, would just kill the fly, so we wanted a system where we could restrict their expression to specific body parts," Perrimon says. "That's what led us to develop this bipartite system, where you have the activated kinase under UAS control in one set of flies, and then you have another set of flies which express the *GAL4* gene in different body parts." When both fly strains are bred with each other, the activated kinase is specifically expressed only in the cells where Gal4 is present.

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 4756 in issue 13 of volume 111.



Signaling pathways control the proliferation of stem cells, shown here intermingled among large enterocytes in the *Drosophila* midgut epithelium. Photo courtesy of M. Markstein and N. Perrimon.

The method's impact on the field is significant. "There are now thousands of *GAL4* fly lines and UAS fly lines that are readily available. The technology took over the field and became part of the *Drosophila* toolbox that everyone is using," Perrimon says. "In fact the original paper we published is one of the most cited papers in the *Drosophila* field, simply because the initial method is still what people use today."

Although the technique has been expanded upon for different uses, including dissecting different brain circuits, the basic system has remained remarkably unchanged. "What's amazing about the Gal4-UAS system is that the method was optimal from the first day," Perrimon says. "The method just worked very well, and the community started to build tools around it, which explains why the Gal4-UAS system has been so popular and now dominates the field."

Perrimon has continued to develop and use new tools and technology throughout his career, and says he's amazed at how much the field has changed. "When I started as a fly geneticist, you couldn't even think about cloning genes," Perrimon says. "Now we can just go and change a single base pair in any gene we want."

Perrimon says he is constantly learning new methods and finding uses for the latest technology. "For example, as the *Drosophila* genome sequence became available around the year 2000, we started to think about large-scale projects to interrogate the genome systematically, and in 2002 we developed high-throughput RNAi screening, where we were able to interrogate the 15,000 *Drosophila* genes in cell-based assays."

"It's a fun time; the tools are incredibly powerful and allow us to get deep insights into the complexity of things," Perrimon says. "But the biological questions aren't changing; it's the same basic questions, it's just that we can address those at an incredibly sophisticated level."

Insights into Signaling

Although Perrimon's early work was focused on discovering genes involved in embryonic development, his focus slowly shifted to studying cell signaling. "As I and my colleagues characterized at the molecular level the genes that we identified, we realized that most of them were involved in signal transduction," he says.

"In fact, we identified components of many different signaling pathways," Perrimon says (5). These included components of the Wingless/Wnt signaling pathways, including molecules that were involved in the secretion and transduction of the Wnt protein. "We also identified components of the JAK/STAT pathway, receptor tyrosine kinase pathways, and so on."

Perrimon has now moved from studying the signaling pathways that orchestrate embryonic development to investigating signaling mechanisms and pathways involved in the communication between organs and tissues. "We are performing a number of different screens to identify pathways involved in the communication between organs," Perrimon says. "These types of screens haven't really been done systematically yet, and the goal is to identify, for example, molecules which communicate the metabolic state of one tissue to another."

For example, Perrimon says he is interested in uncovering how damage to muscle tissues affects the physiology of other tissues, such as fat tissue or the brain. In 2010, Perrimon showed that signaling in the muscles of a fly affects the aging of other tissues (6). More recently, he reported that the state of mitochondria in fly muscle affects the state of mitochondria in other tissues (7).

Another of Perrimon's current projects is to study the regenerative process in the adult *Drosophila* gut. "In this context, what you have is a set of stem cells which proliferate and produce different cells, and the proliferation of stem cells is under the control of a number of different signaling pathways," Perrimon says. "What we don't really understand is the interaction between the different pathways . . . What we're trying to do now is to develop methods that will help us understand the interactions between these signaling pathways."

Modeling the System

Perrimon says he is continually perfecting techniques to precisely study how cells and tissues signal with each other. "Some people in my lab are now developing sensors and genetic tools, which will allow us to visualize signaling with better spatio-temporal resolution. . . . We're particularly interested in understanding how many different signaling pathways cooperate to control a specific biological process, such as the control of stem cell proliferation during regeneration," Perrimon says. "Understanding the integration of different pathways is really a systems biology problem."

The current challenge is to get sufficient spatial and temporal resolution at the single-cell level in complex tissues, Perrimon says. "The limitation is mainly because of the complexity of the systems we are dealing with, and we'd like be able to bring the level of analysis that you can do in single cells to a tissue."

The ultimate goal is to be able to model signaling processes, Perrimon says. "If you understand enough of a biological process, you should be able to mathematically model it using a set of equations that describe what is going on."

"I don't know if it's something we will be able to achieve in 5 years, or 10 years or so," Perrimon says; however, the challenge is what keeps him going.

1 Nüsslein-Volhard C, Wieschaus E (1980) Mutations affecting segment number and polarity in *Drosophila*. *Nature* 287(5785): 795–801.

2 Perrimon N, Gans M (1983) Clonal analysis of the tissue specificity of recessive female-sterile mutations of *Drosophila melanogaster* using a dominant female-sterile mutation Fs(1)K1237. *Dev Biol* 100(2):365–373.

3 Griffin R, Binari R, Perrimon N (2014) Genetic odyssey to generate marked clones in *Drosophila* mosaics. *Proc Natl Acad Sci USA* 111(13):4756–4763.

4 Brand AH, Perrimon N (1993) Targeted gene expression as a means of altering cell fates and generating dominant phenotypes. *Development* 118(2):401–415.

5 Perrimon N, Pitsouli C, Shilo B-Z (2012) Signaling mechanisms controlling cell fate and embryonic patterning. *Cold Spring Harb Perspect Biol* 4(8):a005975.

6 Demontis F, Perrimon N (2010) FOXO/4E-BP signaling in *Drosophila* muscles regulates organism-wide proteostasis during aging. *Cell* 143(5):813–825.

7 Owusu-Ansah E, Song W, Perrimon N (2013) Muscle mitohormesis promotes longevity via systemic repression of insulin signaling. *Cell* 155(3):699–712.