

Linda Van Aelst

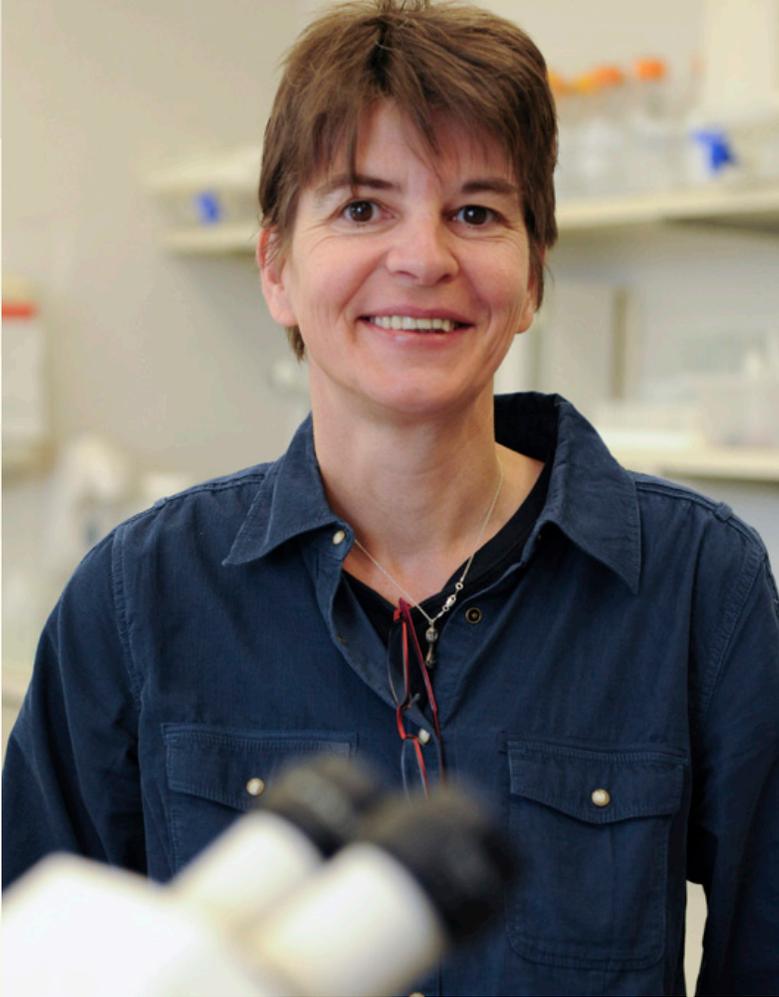
Cell Signaling Opens a Window on Cancer and Brain Disorders

For almost 20 years, Linda Van Aelst has been eavesdropping on Ras-driven chatter in cells of various types, starting with the humble, single-celled yeast and moving all the way up the chain of complexity to various mammalian cell types, including nerve cells found in the brains of mice and rats. By understanding how certain messengers and their messages go awry, she hopes to find ways to restore normal communication in cells that have either strayed down the road to cancer or gone out of sync to give rise to cognitive disorders like autism and mental retardation.

Van Aelst first encountered the Ras protein as a graduate student at Belgium's Catholic University Leuven, one of the oldest universities in Europe. Growing up in Flanders, she had dreamed of becoming either an archeologist or a biologist. "I've always been eager to do a job in which I would discover something new," she says. "Initially, it didn't matter whether I acquired information about the past, present, or the future, as long as it was novel. But eventually, biology won out."

In grad school she began reading reports that described events in cells in which the Ras protein had become mutated. The burning question of the moment: "How did a mutation in the gene that codes for the production of Ras turn normal cells into cancer cells?"

Mutations in three different *ras* genes can be found in roughly one-third of human cancer samples. In some tumor types, the number can be as high as 90%. Although *ras* was found to be an oncogene back in the early 1960s, scientists were still scrutinizing the cell's networks to identify how the Ras protein interacted with so-called downstream partners.



A protein called Ras

Our bodies function properly only because each of our cells is an expert in communication. Cells numbering in the trillions are engaged in a constant talkathon in which scores of molecules take part in signaling networks. These networks pass along messages in the form of chemical reactions that activate, suppress, and modify every aspect of the cell's life and function.

Prominent among these molecular signal transmitters is a protein called **Ras**. Along with other members of an extended "superfamily," Ras participates in what resembles a cellular version of the "telephone" game, whose outcome influences most major cell activities including growth, division, migration, adhesion, and, inevitably, death. So it's no surprise that when Ras and its relatives malfunction — by being too active, acting out of turn, getting messages wrong, or not sending them at all — the cellular mayhem that ensues results in disease of various kinds, many of them potentially catastrophic.

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"We still don't know precisely what the relevant molecules and signaling pathways are for any given type of cancer," says Van Aelst. "This is the kind of information that will help in the design of better, targeted drugs."

The research papers that most excited grad student Van Aelst came from across the Atlantic, from the laboratory of an investigator at Cold Spring Harbor Laboratory named Michael Wigler, who was trying to piece together the daisy chain of proteins that worked downstream of Ras. Meeting Wigler at a scientific conference in Madrid in 1991, Van Aelst had a chance to question him closely about his work.

Above: Postdoc Akiko Kobayashi examines the effect of loss of oligophrenin-1 on the activity of nerve cells in the rat brain.

Facing page: Fruit fly experiments have led postdoc Benjamin Boettner to discover how Rap signaling controls cell shape during growth and movement.

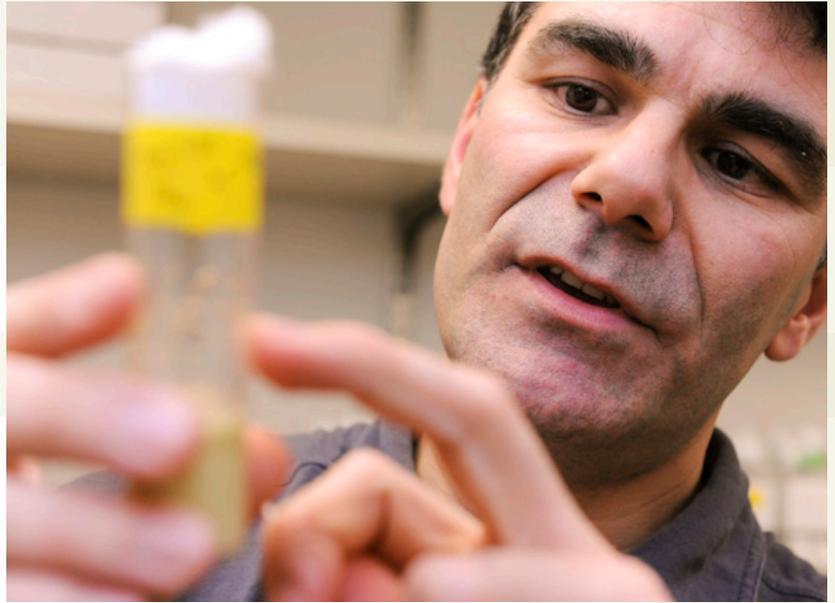
Problems with Ras can lead to cancer

A year or so later, with her doctorate in hand, Van Aelst arrived in Wigler's lab at CSHL for postdoctoral training. Her hunt for Ras's partners produced a quick payoff. Identifying and describing the physical interaction between Ras and another oncoprotein called Raf, her work indicated an important link to a well-known oncogenic network that also involved proteins called MEK and MAP kinases.

Protein kinases are enzymes that modify target proteins by adding phosphate groups to them. Such modifications are an excellent example of the abstract language through which signals are passed along in cells. Ras acts to control "downstream" target proteins by acting as a molecular on/off switch.

When Ras is bound to a protein called GTP, it acts as an "on" switch for the pathway. But once GTP is converted to another protein called GDP, the switch is turned "off." Under normal conditions, Ras and other so-called "GTPases," have to continually cycle between "on" and "off" states to keep the downstream signaling network humming along smoothly.

Van Aelst and colleagues in the Wigler lab showed how gene mutations that lock GTPases in the "on" state can lead to signal distortions causing cells to become cancerous. With her postdoctoral training coming to an end, she mulled a job offer that would have allowed her to return to her native Belgium and a permanent position at the renowned Ludwig Institute. But Wigler and Jim Watson suggested that she stay on at CSHL and start up her own group. Once established at the Laboratory, Van Aelst devoted some of her attention to "relatives" of Ras, including proteins called Rac and Rho. These molecules control pathways that help determine cells' shape, movement and communication. As Van Aelst inched into this new field using new model systems, there were indications that mutations in Rho-associated proteins might be involved in cancer metastasis.



Branching out into neuroscience

All the while, Van Aelst was well aware of research demonstrating the role of Rho proteins in the development of nerve cells in the brain. In the early 2000s, a growing number of mutations associated with Ras and Rho family members and the enzymes that control their activity were found in people suffering from disorders such as autism, neurofibromatosis, and X-linked mental retardation. Van Aelst was especially intrigued to note that some of these proteins were molecules she had identified as Rho's partners in her yeast experiments years earlier.

"It was a good time to expand into a brand new research area," she recalls of the days when she began to educate herself about neuroscience. "It was a big challenge to set up totally new technology to do experiments in a new field. I just had to take a deep breath, expel my fears and go for it."

With Robert Malinow's lab, Van Aelst discovered that Ras and Rap proteins play critical roles at synapses, the tiny junctions across which brain cells communicate. Specifically, they help establish synaptic plasticity — critical changes in the strength of the connection and likely a basis of learning and memory. With Holly Cline,

she discovered that different Rho GTPases regulate distinct aspects of the development of dendrites — the tree-like branching structures found at the ends of neurons that receive signals from other neurons. More recently, the lab has been focusing on a gene called *oligophrenin-1*, which inactivates Rho (see box below).

As deeply entrenched as she is now in studying how Rho GTPase signaling shapes the workings of the brain, Van Aelst hasn't forgotten her cancer-biology roots. With funds from the National Cancer Institute, she is actively pursuing the mechanism by which a signaling "adaptor" called Dok-1 slows down the progression of leukemia and how Ras-related proteins control so-called cell adhesion complexes that are important in tumors.

Far from being a distraction, Van Aelst finds that applying her expertise in two different fields is enriching. "I feel like it has made me more open-minded," she says.



Studying a gene linked to mental retardation

Oligophrenin-1 is one of the genes mutated in people with X-linked mental retardation. In 2004, the Van Aelst team used RNA interference — a technique that silences genes — to "knock down" the expression of this gene in samples of rat brain — thus mimicking the illness in people. Their work showed that *oligophrenin-1* was essential for neurons to develop tree-like dendritic structures of the correct shape and size.

More recently they have shown that the protein made by this gene also seems to play a role in the maintenance of synaptic structure and plasticity. Plasticity refers to the strength of the connection between two neurons. Changes in plasticity are a known basis of brain functions such as learning and memory. By acting on both sides of the synapse, *oligophrenin-1* seems to support long-lasting strengthening in the communication between two simultaneously stimulated neurons that is thought to underlie long-term memory formation and learning.

"We're slowly building a picture of what happens when *oligophrenin-1* is perturbed, particularly with respect to various neuropathologies," Van Aelst explains. "This work is some distance from finding a drug target or a therapeutic solution to these problems, but it's the very necessary step that comes after finding genetic mutations that underlie disease."