Dominique Muller (1956–2015)

On April 29, 2015, the neuroscience community lost an accomplished and beloved scientist when Dominique Muller died in an accident in the French Alps south of Grenoble. He passed away doing his favorite pastime: plane gliding. Dominique had a fiery curiosity that is at the heart of good science. He lived his passion for research in the laboratory, combining experimental creativity, warm mentorship, and public service. His sudden and untimely departure leaves a terrible void.

Dominique was born on February 18, 1956 in Bienne, Switzerland and grew up in Bassecourt, a small village in the Jura, where his father Pierre was a family physician, assisted by Dominique's mother Monique. He started medical school in Geneva in 1975 and obtained his federal diploma in 1981.

Much against his father's expectations, Dominique opted to pursue a career in research rather than as a physician. He started his graduate work in the Department of Pharmacology at the University of Geneva, under the supervision of Yves Dunant, focusing on transmitter release in a very particular experimental model: the *Torpedo* nerve-to-electrocyte junction, a cholinergic synapse in the electric organ of electric rays. Yves recalls that Dominique immediately showed excellence. It was here that he developed an aptitude for studying synaptic physiology and laid a foundation for his future work and interest.

With a newly earned Ph.D. degree (and a family with two young children: Yannick, born in 1982, and Laura, born two years later), Dominique moved to Southern California in 1986, to carry out his postdoctoral training in the laboratory of Garry Lynch. Here, he began to study synaptic plasticity, specifically focusing on long-term potentiation (LTP). During this time, he published several influential papers, each describing a fundamental property of this cellular mechanism that is thought to underlie learning and memory. For example, he showed that LTP is expressed by postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and not N-methyl-D-aspartate receptors (NMDAR), yet it can be induced even when AMPARs are pharmacologically blocked. Thereby, Dominique was one of the first to realize that the induction of LTP could occur in AMPAR-lacking synapses, later to be known as "silent synapses."

With the support of a prestigious Swiss National Science Foundation grant, Dominique was able to return to Geneva, where he would remain active for the rest of his career. Upon his return, he obtained an M.D. degree, and soon after he started to develop his own research lines. He continued working on synaptic LTP, making various important contributions. In collaboration with Kohji Fukunaga, Dominique showed that Ca^{2+}/calmodulin-dependent protein kinase II (CamKII) is activated upon induction of LTP. This corroborated the CaMKII hypothesis as a molecular switch for synaptic plasticity, an influential model that currently continues to receive ample interest in the context of learning and memory. His research team also showed that forms of LTP and long-term depression (LTD) display heterosynaptic interactions, i.e., LTP can reverse LTD or vice versa via separate synaptic pathways.

Dominique Muller, December 2014. Photo credit: Christian Lüscher.

Perhaps one of his most noticeable contributions stems from his work on organotypic slice cultures of the neonatal rat hippocampus. At that time, organotypic neuronal cultures received much interest as an intermediate alternative to the poorly accessible whole brain in vivo and the acute but fleeting brain slice preparation or dissociated cells in vitro. In such cultures, the thickness of the hippocampal slice reduces over time to a few cell layers, which greatly facilitates microscopy of living neurons. It recaptures developmental aspects of neuronal network formation, leaving intact the integrity of the synaptic circuit and preserving the rules for plasticity and activity in shaping network function. Switzerland was being recognized as a hotspot for research in this area by virtue of studies from Beat Gähwiler and colleagues, and Dominique's team continued this tradition. Luc Stoppini, a postdoc in

his laboratory, developed a simplified method for such cultures by using porous, transparent plastic membranes that eliminate the need for plasma clots and roller drums. Because of the simplicity as well as accessibility of the preparation for electrophysiology and optophysiology, the method sparked an immense interest from the larger neuroscience community. Many groups have since adopted this technique, and today the original article describing this approach has been cited more than 2000 times.

Dominique immediately recognized its value and brilliantly exploited the full potential of the technique, which led to a long series of studies investigating molecular and morphological aspects of synaptic plasticity that continued to the day of his passing away. He pioneered studies on morphological changes in dendritic spines, the proxies for excitatory synapses. It was the genius of Dominique that helped develop an electron microscopy (EM) method to visualize activated synapses based on their calcium load. In 1999, with his graduate student Nicolas Toni, Dominique used this method to show that hippocampal LTP induces the formation of new spines that subsequently share presynaptic inputs with neighboring, previously established spines from the same dendrite. This discovery demonstrated that synaptic activity may have long-lasting structural consequences, a feat many others had attempted previously without success. This work not only revealed the incredible structural malleability of nerve cells, it was also a prelude to studies of synaptic clustering, which until today is a poorly understood phenomenon but considered to be important for synaptic circuit function. This original paper published in *Nature* received wide media coverage. One of the very aesthetic figures from this publication was chosen by the Faculty of Medicine for their annual holiday greeting card. It was around this time that he received several prestigious awards, including the Robert Bing prize and the Théodore Ott prize from the Swiss Academy of Medical Sciences, as well as the Max Cloëtta prize. Dominique was modest about the recognition he received, but it illustrates the broad impact of his work.

The finding of synapse ''duplication'' happened in the midst of a burst of research papers on structural synaptic plasticity using live microscopy techniques. The development of two-photon laser scanning microscopy in combination with the use of recombinant fluorescent proteins allowed researchers to study neurons and synapses in real time in scattering tissue. Luc and Dominique's culture technique became instrumental in these pioneering studies that have since then generated an overwhelming source of information on synaptic structure-function relationships. The preparation became an even more powerful tool when biolistic gene transfer techniques, until then used in plant biological sciences, became applicable to mammalian cells in vitro.

Dominique embraced these new tools and applied them to investigate what interested him most: the molecular basis for changes in synaptic function and structure. Together with colleagues at the University of Geneva he discovered key roles for cell adhesion molecules (NCAM and N-cadherins) in neuronal and synaptic plasticity. With Irina Nikonenko, a long-term collaborator in his lab, he pioneered the use of correlated serial section EM and confocal imaging in organotypic slices for reconstructing fluorescently labeled and previously imaged neurons in order to reveal relationships between synaptic function and ultrastructural features of synapses. This led to various new insights into the behavior of pre- and postsynaptic components during synaptic plasticity. These self-initiated new avenues in synaptic research prompted Dominique to commence studies toward the relationship between changes in synaptic structure-function and intellectual disabilities, such as X-linked mental retardation. He recently became interested in the molecular and structural underpinnings of neuropsychiatric diseases. To approach these complex questions, he enthusiastically participated in various Swiss and European collaborative networks. He was instrumental in the development of ''Synapsy'', one of the Swiss National Centers for Competence in Research, focusing on unifying research of neuropsychiatric disorders. He codirected this large-scale network with his long-time colleague and friend Pierre Magistretti. He was an active member of various Swiss National Science Foundation committees and treasurer of the FENS forum in 2008. He helped create the Geneva Center for Neuroscience, as well as the Lemanic Neuroscience Doctoral School, a communal graduate program in Neuroscience shared between the Universities of Lausanne and Geneva, which he codirected from 2002 until 2011.

Since 2008, Dominique headed the Department of Basic Neuroscience at the Faculty of Medicine, which he helped establish in 2003. He was a chairman with great vision, a charismatic group leader, and an amiable colleague. He promoted excellence and competitiveness but also had the ability to resonate with the needs of his colleagues. His style of leadership was based on respect and generosity. Despite high administrative workload, he managed to spend time in the lab doing experiments. It was during these weekly experimental sessions that one would catch Dominique at his happiest. He lived for the experimental work and considered the administrative part of his job as an ancillary but necessary task that he fulfilled out of a responsibility he felt toward the neuroscience community in Geneva—a thriving community that he helped to build. Throughout his career, he earned great respect from his students and colleagues for his passion for science and education, his considerateness, and his support of young and upcoming scientists. He was still full of ambitious, promising, and innovative ideas. With his death ends—unfortunately far too early—an exemplary scientific career. We console ourselves with the thought that his ideas have greatly influenced countless scientists around the world and that Dominique's spirit will survive through their work.

Dominique is survived by his wife Harriët, his children Yannick and Laura, now working as M.D.-Ph.D. and M.D., respectively at the Geneva University Hospital, two grandchildren, and his mother Monique.

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