Daniela Pietrobon
Curriculum vitae

Education and training

1979, University of Padova, Degree (Laurea) in Chemistry, Magna cum Laude.
1979-1982, Research Fellow (Lab. Prof. G. Azzone), Institute of General Pathology, University of Padova: Energy transduction in mitochondria.
1984-1985, Postdoctoral Fellow (two EMBO Short Term Fellowships), Dept of Membrane Research (lab. Prof. R. Caplan), Weizmann Institute of Science, Israel: Non-equilibrium thermodynamics of oxidative phosphorylation and kinetic modelling of mitochondrial H+ pumps.
1987-1990, Postdoctoral Fellow (EMBO Long Term Fellowship and Fogarty International Fellowship), Dept of Cellular and Molecular Physiology (Lab Prof P. Hess), Harvard Medical School, U.S.A.: Biophysics of voltage-gated Ca^{2+} channels.

Employment and Research experience

1983-1991, CNR Researcher, CNR Unit Physiology of Mitochondria, Institute of General Pathology, University of Padova: Energy transduction in mitochondria.
1991-1993, CNR Director of Research, CNR Unit Physiology of Mitochondria, Dept. of Biomedical Sciences, Univ. of Padova: Biophysics and physiology of neuronal Ca^{2+} channels.
1993-2000 Associate Professor of General Physiology (Faculty of Sciences), Dept. of Biomedical Sciences, Univ. of Padova: Biophysics and physiology of neuronal Ca^{2+} channels.
2000-present, Professor of Physiology, Dept. of Biomedical Sciences, Univ. of Padova: Calcium channelopathies of the central nervous system, in particular familial hemiplegic migraine; migraine pathophysiology.

Honors and Professional Memberships and Committees

1985, Luigi Galvani Prize of the Bioelectrochemical Society.
1996-2000 Member of Council of the Italian Society of Pure and Applied Biophysics
1996-2002 Member of Council of IUPAB (Int. Union of Pure and Applied Biophysics)
2000-2003, Coordinator of the PhD Program in Molecular and Cellular Biology and Pathology of the Univ. of Padova.
2001, National Prize “President of the Republic” in Mathematical, Physical and Natural Sciences awarded by the Accademia dei Lincei
2005-2015, Coordinator of the PhD Program in Neurobiology within the PhD School of Biosciences of the Univ of Padova
2006-2011 Editorial Board of “The Journal of Physiology”
2007- Editorial Board of “Channels”.
2010- Member of Faculty of 1000
2011- Member of the Venetian Institute of Letters, Arts and Sciences
2016- Editorial Board of “Neuroscience”
2017- invited to Editorial Board of “European Journal of Physiology”

Invited speaker at the following international congresses in the last 5 years:

FASEB Conference on Ion Channel regulation (2013)
International Union of Physiological Societies Congress (IUPS) (Keynote Lecture, 2013)
24th Ion Channel Meeting of the French Association of Ion Channels (2013)
9th FENS Forum of Neuroscience (2014)
15th World Congress on Pain (2014)
Mini-symposium on Migraine Disorders (2015)
Winter Conference on Neural Plasticity (2015)
2nd European Calcium Channel Conference (2015)
COSBID 2016 (2016) Keynote lecture
Conference "More than neurons: towards a less neurocentric view of brain disorders" (2016)

Acts as **referee** for many prestigious scientific journals (including Science, Neuron, PNAS, eLife, Ann Neurol, J Neurosci, J Physiol) and international granting agencies (including: Human Frontier Science Program, Wellcome Trust Foundation, National Institute of Health, NIH, ANR, Israel Science Foundation).

Contribution to Science (and selected publications)

1. **Functional consequences of mutations causing familial hemiplegic migraine and migraine pathophysiology**

Familial Hemiplegic Migraine type 1 (FHM1). We characterized the effect of several FHM1 mutations on the biophysical properties of human recombinant CaV2.1 channels expressed in both heterologous systems and neurons. We demonstrated that the mutations increase the open probability and shift the activation of the calcium channel to lower voltages and hence produce gain-of-function of the human $Ca_V2.1$ channel (1-3). Later, we characterized the functional consequences of FHM1 mutations on neuronal calcium channels, cortical synaptic transmission and cortical spreading depression in FHM1 knockin mice. We confirmed the gain-of-function of the calcium current in several neurons of FHM1 mice including cortical pyramidal neurons (4-7), but also showed that in specific types of neurons, including cortical fast-spiking interneurons, the calcium current was barely affected (7-8). We showed that cortical excitatory synaptic transmission and glutamate release at cortical pyramidal cell synapses were enhanced in FHM1 mice, whereas, in striking contrast, inhibitory synaptic transmission and GABA release were unaltered at fast-spiking and other multipolar interneuron synapses (5, 8-9). We demonstrated a lower threshold for induction of cortical spreading depression (CSD) and a higher rate of CSD propagation in FHM1 mice both in vivo and in cortical slices (4-6), and showed that the facilitation of CSD in these mice is due to the excessive release of glutamate from cortical excitatory synapses (5).

Familial Hemiplegic Migraine type 2 (FHM2). More recently, we characterized the functional consequences of a FHM2 mutation on glutamate and K+ clearance by cortical astrocytes in heterozygous FHM2 knockin mice with reduced expression of the α2 Na, K ATPase and revealed that i) the reduced expression of the α2 Na, K ATPase leads to a similar reduction in the membrane expression of the glutamate transporter GLT1 in perisynaptic astrocytic processes surrounding cortical glutamatergic synapses and ii) the rates of glutamate and K+ clearance by cortical astrocytes are both reduced in FHM2 mice (10). We demonstrated a lower threshold for CSD induction and a higher rate of CSD propagation in FHM2 knockin mice both in vivo and in cortical

slices (10, 11), and showed that the reduced rate of glutamate clearance by astrocytes can account for a large fraction of the facilitation of CSD induction and propagation in these mice (10).

1. M. Hans, S. Luvisetto, M.E. Williams, M. Spagnolo, A. Urrutia, A. Tottene, P.F. Brust, E.C. Johnson, M.M. Harpold, K.A. Stauderman and **D. Pietrobon**. Functional consequences of mutations in the human α1A calcium channel subunit linked to familial hemiplegic migraine. **J Neurosci** (1999) 19, 1610-1619.

2. A. Tottene, T. Fellin, S. Pagnutti, S. Luvisetto, J. Striessnig, C. Fletcher and **D. Pietrobon.** Familial hemiplegic migraine mutations increase Ca2+ influx through single human $Ca_V2.1$ channels and decrease maximal $Ca_V2.1$ current density in neurons. **Proc Natl Acad Sci** (2002) 99, 13284-13289.

3. A. Tottene, F. Pivotto, T. Fellin, T. Cesetti, A.M.J.M. van den Maagdenberg and **D. Pietrobon.** Specific kinetic alterations of human $Ca_V2.1$ calcium channels produced by mutation S218L causing familiar hemiplegic migraine and delayed cerebral edema and coma after minor head trauma. **J Biol Chem** (2005) 280, 17678-17686.

4. A.M.J.M. van den Maagdenberg*, **D. Pietrobon***, T. Pizzorusso, S. Kaja, L.A.M. Broos, T. Cesetti, R.A.G. van de Ven, A. Tottene, J. van der Kaa, J.J. Plomp, R.R. Frants, M.D. Ferrari. A cacna1a knockin migraine mouse model with increased susceptibility to cortical spreading depression. **Neuron** (2004) 41, 701-710
*Shared first authorship and shared corresponding authorship.

5. Tottene A., Conti R., Fabbro A, Vecchia D, Shapovalova M, Santello M, van den Maagdenberg AMJM, Ferrari M and **Pietrobon D** Enhanced excitatory transmission at cortical synapses as the basis for facilitated spreading depression in CaV2.1 knockin migraine mice. **Neuron** (2009) 61: 762-773

6. Van den Maagdenberg AMJM*, Pizzorusso T, Kaja S, Terpolilli N, Shapovalova M, Hoebeek FE, Barrett CF, Gherardini L, van de Ven RC, Todorov B, Broos LAM, Tottene A, Gao Z, Fodor M, De Zeeuw CI, Frants RR, Plesnila N, Plomp JJ, **Pietrobon D*** and Ferrari MD. High cortical spreading depression susceptibility and migraine-associated symptoms in $Ca_V2.1$ S218L mice. **Ann. Neurol.** (2010) 67:85-98.
* Shared corresponding authorship

7. Fioretti B, Catacuzzeno L, Sforna L, Gerke-Duncan MB, van den Maagdenberg AM, Franciolini F, Connor M, **Pietrobon D**. Trigeminal ganglion neuron subtype-specific alterations of Ca(V)2.1 calcium current and excitability in a Cacna1a mouse model of migraine. **J Physiol** (2011) 589: 5879-5895

8. Vecchia D, Tottene A, van den Maagdenberg AM, **Pietrobon D**. Mechanism underlying unaltered cortical inhibitory synaptic transmission in contrast with enhanced excitatory transmission in $Ca_V2.1$ knockin migraine mice. **Neurobiol Dis** (2014) 69:225-34

9. Vecchia D, Tottene A, van den Maagdenberg AM, **Pietrobon D**. Abnormal cortical synaptic transmission in CaV2.1 knockin mice with the S218L missense mutation which causes a severe familial hemiplegic migraine syndrome in humans. **Front. Cell. Neurosci.** (2015) 9:8; doi: 10.3389

10. Capuani C, Melone M, Tottene A, Bragina L, Crivellaro G, Santello M, Casari G, Conti F, **Pietrobon D**. Defective glutamate and K+ clearance by cortical astrocytes in familial hemiplegic migraine type 2. **EMBO Mol Med.** (2016) 8:967-86

11. Leo L, Gherardini L, Barone V, De Fusco M, **Pietrobon D**, Pizzorusso T, Casari G. Increased susceptibility to cortical spreading depression in the mouse model of familial hemiplegic migraine type 2. **PLoS Genet** (2011) 7(6):e1002129

We were asked to write several **reviews on familial hemiplegic migraine and migraine mechanisms** (12-18), and recently a review on **cortical spreading depression** (19).

12. **D. Pietrobon** and J. Striessnig. Neurobiology of Migraine. **Nature Rev Neurosci** (2003) 4, 386-398

13. **D. Pietrobon.** Migraine: New Molecular Mechanisms. **Neuroscientist** (2005) 11, 373-386.

14. **D. Pietrobon.** Familial Hemiplegic Migraine**. Neurotherapeutics** (2007) 4, 274-284

15. **D. Pietrobon.** Insights into migraine mechanisms and $Ca_V2.1$ channel function from animal models of familial hemiplegic migraine. **J Physiol** (2010) 588: 1871-1878

16. Vecchia D and **Pietrobon D**. Migraine: a disorder of brain excitatory-inhibitory balance? **Trends Neurosci.** (2012) 35:507-520

17. **Pietrobon D.** Calcium channels and migraine. **Biochim Biophys Acta** (2013) 1828:1655-65.

18. **Pietrobon D** and Moskowitz M. Pathophysiology of migraine. **Ann Rev Physiol** (2013) 75:365-91

19. **Pietrobon D** and Moskowitz M. Propagation of chaos and commotion in the wake of cortical spreading depression and spreading depolarizations. **Nature Rev. Neurosci.** (2014) 15:379-93

2. $Ca_V2.1$ channelopathies

Before concentrating on FHM we studied the functional consequences of mutations in the CACNA1A gene causing episodic ataxia type 2 (EA2) and the functional consequences of knocking out the $Ca_V2.1$ channel in mice. We demonstrated that EA2 mutations cause loss-of-function of $Ca_V2.1$ channels (20). In $Ca_V2.1$-/- mice, we showed dystonia and cerebellar atrophy in a highly specific pattern (21), and by analyzing pain-related behavioral responses we revealed a pronociceptive role of $Ca_V2.1$ channels in inflammatory and neuropathic pain states (22). We wrote several reviews on $Ca_V2.1$ channelopathies (23-26).

20. S. Guida, F. Trettel, S. Pagnutti, E. Mantuano, A. Tottene, L. Veneziano, T. Fellin, M. Spadaro, K. Stauderman, M.E. Williams, S. Volsen, R.A. Ophoff, R.R. Frants, C. Jodice, M. Frontali and **D. Pietrobon** Complete loss of P/Q calcium channel activity caused by a CACNA1A missense mutation carried by patients with episodic ataxia type 2. **Am J Hum Genet** (2001), 68, 759-764

21. C. Fletcher*, A. Tottene*, V.A. Lennon, S.M. Wilson, S.J. Dubel, R. Paylor, D.A. Hosford, L. Tessarollo, M.W. McEnery, **D. Pietrobon**, N.G. Copeland and N. A. Jenkins Dystonia and cerebellar atrophy in Cacna1a null mice lacking P/Q calcium channel activity. **FASEB J** (2001), 15, 1288-1290

* Shared first authorship

22. S. Luvisetto, S. Marinelli, M.S. Panasiti, F.R. D'Amato, C.F. Fletcher, F. Pavone and **D. Pietrobon**. Pain sensitivity in mice lacking the Ca(v)2.1alpha1 subunit of P/Q-type Ca2+ channels. **Neuroscience** (2006) 142, 823-32.

23. **D. Pietrobon.** Calcium channels and channelopathies of the central nervous system. **Mol Neurobiol** (2002) 25, 13-32.

24. **D. Pietrobon.** Function and dysfunction of synaptic calcium channels: insights from mouse models**. Curr Opin Neurobiol** (2005) 15, 257-269

25. Catterall WA, Dib-Hajj S, Meisler MH and **Pietrobon D.** Inherited Neuronal Ion Channelopathies: New Windows on Complex Neurological Diseases. **J. Neurosci**. (2008) 28:11768-11777

26. **Pietrobon D.** $Ca_V2.1$ channelopathies. **Pfluegers Arch**. (2010) 460:375-393.

3. Biophysical properties of voltage-gated Ca^{2+} channels and the molecular and functional diversity of neuronal Ca2+ channels

Before getting interested in $Ca_V2.1$ channelopathies, we used single channel current recordings to characterize i) the biophysical properties of cardiac voltage-gated L-type Ca^{2+} channels and of recombinant human $Ca_V2.1$ channels and ii) the functional diversity of neuronal Ca^{2+} channels. We discovered a new mechanism of regulation of the conductance of L-type Ca^{2+} channels by protons (27-30) and a new mechanism of voltage-dependent gating of L-type Ca^{2+} channels (31). Moreover we revealed different gating modes of human $Ca_V2.1$ channels (32-33). We discovered a new "anomalous" neuronal voltage-gated L-type Ca^{2+} channel and characterized its biophysical and molecular properties (34-36). We also revealed a novel neuronal P-type and two novel neuronal R-type Ca2+ channels (37-39).

27. B. Prod'hom, **D. Pietrobon** and P. Hess. Direct measurement of proton transfer rates to a group controlling the dihydropyridine-sensitive Ca2+ channel. **Nature** (1987) 329, 243-246

28. **D. Pietrobon**, B. Prod'hom and P. Hess. Conformational changes associated with ion permeation in L-type calcium channels. **Nature** (1988) 333, 373-376

29. **D. Pietrobon**, B. Prod'hom and P. Hess. Interactions of protons with single open L-type calcium channels. pH dependence of proton induced current fluctuations with Cs+, K+ and Na+ as permeant ions". **J Gen Physiol** (1989) 94, 1-21

30. B. Prod'hom, **D. Pietrobon** and P. Hess. Interactions of protons with single open L-type calcium channels. Location of protonation site and dependence of proton-induced current fluctuations on concentration and species of permeant ion. **J Gen Physiol** (1989) 94, 23-42

31. **D. Pietrobon** and P. Hess. Novel mechanism of voltage-dependent gating in L-type calcium channels. **Nature** (1990) 346, 651-655

32. S. Luvisetto, T. Fellin, M. Spagnolo, B. Hivert, PF Brust, M.M. Harpold, K.A. Stauderman, M.E. Williams and **D. Pietrobon.** Modal Gating of Human CaV2.1 (P/Q-type) Calcium Channels: I. The Slow and the Fast Gating Modes and their Modulation by {beta} Subunits. **J Gen Physiol**. (2004) 124, 445-461.

33. T. Fellin, S. Luvisetto, M. Spagnolo, and **D. Pietrobon.** Modal Gating of Human CaV2.1 (P/Q-type) Calcium Channels: II. The b Mode and Reversible Uncoupling of Inactivation. **J Gen Physiol.** (2004) 124, 463-74.

34. L. Forti and **D. Pietrobon.** Functional diversity of L-type calcium channels in rat cerebellar neurons. **Neuron** (1993) 10, 437-450

35. B. Hivert, S. Luvisetto, A. Navangione, A. Tottene and **D. Pietrobon.** Anomalous L-type calcium channels of rat spinal motoneurons**. J Gen Physiol** (1999) 113, 679-693

36. Koschak A, Obermair GJ, Pivotto F, Sinneger-Brauns MJ, Striessnig J and **Pietrobon D.** Molecular nature of anomalous L-type calcium channels in mouse cerebellar granule cells. **J. Neurosci.** (2007) 27:3855-3863

37. L. Forti, A. Tottene, A. Moretti and **D. Pietrobon.** Three novel types of voltage-dependent calcium channels in rat cerebellar neurons. **J Neurosci** (1994) 14, 5243-5256

38. A. Tottene, A. Moretti and **D. Pietrobon.** Functional diversity of P-type and R-type calcium channels in rat cerebellar neurons. **J Neurosci** (1996) 16, 6353-6363.

39. A. Tottene, S. Volsen and D. Pietrobon**.** α1E subunits form the pore of three cerebellar R-type calcium channels with different pharmacological and permeation properties. **J. Neurosci.** (2000) 20, 171-178

4. Biophysical properties of mitochondrial proton pumps and energy transduction in mitochondria.

At the beginning of my scientific career I combined experiments and modelling to investigate the biophysical mechanisms of coupling between electron transfer and proton translocation in mitochondrial redox-driven proton pumps and between ATP synthesis-hydrolysis and proton translocation in mitochondrial proton ATPases, and the role of the H+ electrochemical gradient across the inner mitochondrial membrane in mitochondrial energy transduction. We revealed that the mitochondrial proton pumps are incompletely coupled (40-42) and that classical mitochondrial uncouplers induce pump "slippage" besides acting as protonophores (43), and developed detailed kinetic models of the mitochondrial H+ pumps and their chemiosmotic coupling (44-49)

40. **D. Pietrobon**, G.F. Azzone and D. Walz. Effect of funicolosin and antimycin A on the redox-driven H^+-pumps in mitochondria: on the nature of leaks. **Eur J Biochem** (1981) 117, 389-394

41. **D. Pietrobon**, M. Zoratti, G.F. Azzone, J.W. Stucki and D. Walz. Non equilibrium thermodynamic assesment of redox-driven H+ pumps in mitochondria. **Eur J Biochem** (1982) 127, 483-494

42. **D. Pietrobon**, M. Zoratti and G.F. Azzone. Molecular slipping in redox and ATPase H^+-pumps. **Biochim Biophys Acta** (1983) 723, 317-321

43. **D. Pietrobon**, S. Luvisetto and G.F. Azzone. Uncoupling of oxidative phosphorylation. 2) Alternative mechanisms: intrinsic uncoupling or decoupling?. **Biochemistry** (1987) 26, 7339-7347

44. **D. Pietrobon** and S.R. Caplan. Flow-force relationships for a six-state proton pump model: intrinsic uncoupling, kinetic equivalence of input and output forces, and domain of approximate linearity. **Biochemistry** (1985) 24, 5764-5776

45. **D. Pietrobon.** A non linear kinetic model of chemiosmotic energy coupling. **Bioelectrochem Bioenerg** (1986) 15, 193-209

46. **D. Pietrobon**, M. Zoratti, G.F. Azzone and S.R. Caplan. Intrinsic uncoupling of mitochondrial proton pumps. II. Modelling studies. **Biochemistry** (1986) 25, 767-775

47. **D. Pietrobon** and S.R. Caplan. Double inhibitor and uncoupler-inhibitor titrations. I. Analysis with a linear model of chemiosmotic energy coupling. **Biochemistry** (1986) 25, 7682-7690

48. **D. Pietrobon** and S.R. Caplan. Double inhibitor and uncoupler-inhibitor titrations. II. Analysis with a nonlinear model of chemiosmotic energy coupling. **Biochemistry** (1986) 25, 7690-7696

49. S.R. Caplan and **D. Pietrobon**. Theoretical analysis of double-titrations experiments. **Biochim Biophys Acta** (1987) 895, 241-258

Bibliometric indicators

h index: 42 (Google Scholars); 41 (Scopus)

total citations: 6836 (Google Scholars); 5160 (Scopus)

citations/paper: 100.5 (Google Scholars); 71.7 (Scopus)

total IF: 561

IF/paper: 7.8