DEMAUREX Nicolas, 1963

CURRICULUM VITAE

1. Personal data

Name:	**DEMAUREX Nicolas**
Born:	March 26, 1963
Nationality:	Swiss
Marital Status:	Married, three children
Academic Grade	Professor, University of Geneva

Address: Department of Cell Physiology and Metabolism
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2. Current Position

Full professor, Department of Cell Physiology and Metabolism, Geneva, Switzerland
Teaching 20%, research 60%, administration 20%

3. Education

1982-89	Medical School, University of Geneva, Switzerland
1993	Thesis in Medicine, University of Geneva, Switzerland
1993	Thesis in Biological Sciences, University of Geneva, Switzerland
2001	Privat-Docent, Faculty of Medicine, University of Geneva

4. Professional Activities

1989-93	PhD Fellow, Infectious Diseases, Geneva University Hospitals (Prof. D. Lew)
1994-96	Post-Doctoral Fellow, Division of Cell Biology, Hospital for Sick Children, Toronto, Canada (Prof. S. Grinstein)
1996-97	Maître Assistant, Medical Research Foundation Geneva (Prof. W. Schlegel)
1997-03	Max Cloëtta fellow, Dept. of Physiology, University of Geneva, Switzerland
2004	Associate Professor, Dept. of Cell Physiology and Metabolism, University of Geneva, Switzerland
2010	Full Professor, Dept. of Cell Physiology and Metabolism, University of Geneva, Switzerland
2012	Vice-dean, faculty of medicine, University of Geneva

5. Teaching:

Pregraduate:

1997-	Faculty Tutor for 2nd and 3rd year Medical Students (28 h/year)
2000-2013	co-organizer, Problem-based teaching unit « Excretion and Homeostasis »
2009-	Course on membrane transport, 1st year Medical Students (8h/year)

Postgraduate:

1999-	Instructor, post-graduate course in Cell and Molecular Biology (30h/year)
2003	Organizer, Cell Imaging Course, Swiss Federal Institute of Technology (96h)

6. Awards

1993	Award from the *Swiss Society of Infectious Diseases*
1997	Career award from the *Max Cloëtta* Foundation, Zürich
1999	Research Award from the *Leenaards* Foundation, Lausanne

7. Membership of Scientific Societies

2015-2018 President of the Physiology section, Society of Life Sciences Switzerland (LS2)

8. Official Fonctions

2006-2010 Chair, Department of Cell Physiology and Metabolism, University of Geneva
2012- Vice-dean, faculty of medicine, University of Geneva
2012- Member of the Federal Committee for Medical Professions (MEBEKO)

9. Editorial Work

Editorial adviser: *Biochem J.*, Regular referee: *J. Biol. Chem., J. Physiol.* Ad hoc referee: *Cell, Science, Nature, PNAS, EMBO J., J.Clin. Invest, J. Immunol, J.Exp. Med, J. Cell Biol, J. Cell Science, J. Gen. Physiol., Am. J. Physiol., Mol. Biol. Cell; Eur. J. Physiol., Biochem. Biophys. Acta; Mol. Biol. Cell, Cell Death and Differentiation, Cell Calcium, J. Leuk. Biology*

10. Grants (in bold: active)

1996-1999 SNF 31-46859 "Calcium homeostasis of the Golgi complex CHF 297'000.-
1999-2002 SNF 31-56802 "Calcium homeostasis of intracellular organelles and proton conductances" CHF 320'000.-
2002-2007 SNF 31-068317 "Role of mitochondria in calcium signalling and apoptosis. Identification and characterization of proton channels" CHF 798'000.-
2007-2010 SNF 31003A_118393 "Signalling proteins and ion channels of the endoplasmic reticulum, mitochondria, and phagosomes" CHF 479'000.-
2010-2013 SNF 31003B_133126 "Signalling proteins and ion channels of the endoplasmic reticulum, mitochondria, and phagosomes" CHF 521'294.-
2013-2016 SNF 31003A_149566 "Signalling at membrane contact sites between the endoplasmic reticulum, mitochondria, and phagosomes" CHF 751'000.-
2015-2017 COST BM1406 "Voltage-gated proton channel Hv1 inhibitors: mode of action and impact on immune functions" (SEFRI C15.0035) CHF 180'000.-
2015-2018 Sinergia CRSII3_160782 "Store-operated calcium channels in health and disease" (main applicant: Matthias Hediger) CHF 1'665'788.-
2016-2019 SNF 31003A_169491 "Calcium signaling at membrane contact sites during phagocytosis" CHF 429'000.-
2017-2020 CTI 26125.1 "Targeting Hv1 proton channels: an innovative therapy for B-cell malignancies" (R&D project with HPlus Therapeutics) CHF 607.334-
2019-2023 SNF 310030_189042 "Calcium signaling at membrane contact sites during phagocytosis" CHF 632'000.-

The major goals of this grant are to define the role of the calcium signaling proteins STIM1 and Orai1 in the regulation of phagocytosis, a fundamental cellular process essential for innate and acquired immunity.

11. Thesis supervision

Completed: Andrès Maturana (UNIGE Biology, 2002), Hélène Jousset (UNIGE Biology, 2007), Nathalie Girardin (UNIGE Biology, 2010), Samira Daou (Uni Versailles Bacteriology, 2011), WeiWei Shen (UNIGE Biology, 2012), Yves Gouriou (UNIGE Neurosciences, 2013), Daniele Guido (UNIGE Biology, 2016), Sophie Saüc (UNIGE Biology, 2017), Monica Bulla (UNIGE MD-Ph.D, 2018), Christopher Henry(2021), Ongoing: Mayis Kaba (2017-), Camille Rabesahala de Meritens (2020-) Raphael Neré (2022-)

Group members: Amado Carreras-Sureda, Senior lecturer; Sana Kouba, Nicolas Rosa, Xin Zhang, post-docs; Mayis Kaba, Camille Rabesahala de Meritens, Raphael Neré. Ph.D students; Cyril Castelbou, technician

12. Research focus

Cell signalling; physiology of ion transport

MAJOR SCIENTIFIC ACHIEVEMENTS:

My research focuses on the mechanisms controlling the calcium and pH homeostasis of innate immune cells, with a particular focus on store-operated Ca^{2+} signaling. Store-operated Ca^{2+} entry (SOCE) channels are found in the plasma membrane of all animal cells and are activated through a decrease in the Ca^{2+} concentration in the endoplasmic reticulum (ER). In immune cells, SOCE generates Ca^{2+} signals important for gene expression, proliferation, and the secretion of inflammatory mediators. My laboratory was instrumental in establishing the molecular basis and significance of membrane contact sites generated between the ER and the plasma membrane during SOCE and we have made several important contributions towards understanding the role of Ca^{2+} signaling in regulating the functions of neutrophils and dendritic cells. Current efforts in the laboratory are focused on understanding the physiological roles of ion channels in sustaining the migration and bactericidal activity of white blood cells. We use a multifaceted approach for these studies that combines mouse genetics, electrophysiology, electron microscopy, and a variety of imaging techniques. My main contributions to science have addressed the following topics:

1) ***Calcium signaling at membrane contact sites.*** *We have characterized the molecular and ultrastructural basis of the membrane contact sites generated by the regulatory protein STIM1 and established the physiological relevance of STIM1-mediated signaling for phagocytosis, a fundamental cellular process essential for innate and acquired immunity.*

Henry C, Carreras-Sureda A & Demaurex N. Enforced tethering elongates the cortical endoplasmic reticulum and limits store-operated calcium entry. J. Cell Sci (2022) 135: jcs259313. doi:10.1242/jcs.259313

Nunes-Hasler P, Maschalidi S, Lippens C, Castelbou C, Bouvet S, Guido D, Bermont F, Bassoy EY, Page N, Merkler D, Hugues S, Martinvalet D, Manoury B, & Demaurex N. STIM1 promotes migration, phagosomal maturation and antigen cross-presentation in dendritic cells. Nat Commun 8:1852 (2017)

Guido D, Demaurex N[1]. & Nunes P[1]. Junctate boosts phagocytosis by recruiting endoplasmic reticulum Ca2+ stores near phagosomes. J. Cell Sci 128:4074-82 (2015) [1]Equal contribution

Sauc S, Bulla M, Nunes P, Orci L, Marchetti A, Antigny F, Bernheim L, Cosson P, Frieden, & Demaurex N. STIM1L traps and gates Orai1 channels without remodeling the cortical ER. J. Cell Sci 128:1568-79 (2015).

Nunes P, Cornut D, Bochet V, Hasler U, Oh-Hora M, Waldburger J-M, & Demaurex N. STIM1 Juxtaposes ER to Phagosomes, Generating Ca2+ Hotspots that Boost Phagocytosis. Current Biology 22:1990-7 (2012).

Orci L, Ravazzola M, Le Coadic M, Shen W, Demaurex N, & Cosson P. STIM1-induced pre-cortical and cortical subdomains of the endoplasmic reticulum PNAS 106:19358-62 (2009)

2) ***Physiological regulation of store-operated calcium entry****. We have discovered new regulatory pathways controlling STIM1-gated Orai channels and characterized natural mutations in these genes associated with human pathologies.*

Kim JH, Carreras-Sureda A, Didier M, Henry C, Frieden M, Demaurex N. The TAM-associated STIM1I484R mutation increases ORAI1 channel function due to a reduced STIM1 inactivation break and an absence of microtubule trapping. Cell Calcium 105:102615 (2022). doi:10.1016/j.ceca.2022.102615.

Wang WA, Demaurex N. The mammalian trafficking chaperone protein UNC93B1 maintains the ER calcium sensor STIM1 in a dimeric state primed for translocation to the ER cortex. J. Biol. Chem. (2022) doi: 10.1016/j.jbc.2022.101607

Carreras-Sureda A, Abrami L, Kim JH, Wang WA, Henry C, Frieden M, Didier M, van der Goot F, Demaurex N. S-acylation by ZDHHC20 targets ORAI1 channels to lipid rafts for efficient Ca 2+ signaling by Jurkat T cell receptors at the immune synapse. Elife. 10:e72051 (2021). doi:10.7554/eLife.72051

Bulla M, Gyimesi G, Kim JH, Bhardwaj R, Hediger MA, Frieden M, & Demaurex N. ORAI1 channel gating and selectivity is differentially altered by natural mutations in the first or third transmembrane domain. J. Physiol. 597:561-582 (2019)

*3) **Calcium homeostasis of mitochondria.** We have established the role of mitochondria in shaping the pattern of cellular calcium signals and in mediating the calcium refilling of the endoplasmic reticulum.*

Poburko D, Liao CH, van Breemen C, & Demaurex N. Mitochondrial regulation of SR Ca2+ content in vascular smooth muscle cells. Circ Res. 104:104-12 (2009).

Frieden M, Arnaudeau S, Castelbou C, & Demaurex N. Subplasmalemmal mitochondria modulate the activity of plasma membrane Ca2+ ATPases. J. Biol. Chem. 280:43198-208 (2005).

Frieden M, James D, Castelbou C, Danckaert A, Martinou J-C, Demaurex N. Calcium homeostasis during mitochondrial fragmentation and perinuclear clustering induced by hFis1. J. Biol. Chem. 279:22704-14 (2004).

Arnaudeau S, Kelly WL, Walsh JV Jr, & Demaurex N. Mitochondria recycle Ca2+ to the endoplasmic reticulum and prevent the depletion of neighboring ER regions J. Biol. Chem. 276: 29430-9 (2001).

*4) **Calcium regulation of mitochondria redox and pH homeostasis.** We have identified and characterized molecular determinants regulating activity-dependent changes in mitochondria metabolic parameters.*

Rosselin M, Nunes-Hasler P& Demaurex N. Ultrastructural characterization of flashing mitochondria. Contact 1: 1-14 (2018)

Rosselin M, Santo-Domingo J, Bermont F, Giacomello M, & Demaurex N. L-OPA1 regulates mitoflash biogenesis independently from membrane fusion. EMBO Reports 18:451-63 (2017).

De Marchi U, Santo Domingo J, Castelbou C, Sekler I, Wiederkehr A, Demaurex N. NCLX, but not LETM1, mediates mitochondrial Ca2+ extrusion thereby limiting Ca2+-induced NAD(P)H production and modulating matrix redox state. J. Biol. Chem. 289:20377-85 (2014).

Santo-Domingo J, Giacomello M, Poburko D, Scorrano L, & Demaurex N. OPA1 promotes pH flashes that spread between contiguous mitochondria without matrix protein exchange. EMBO J. 32:1927-40 (2013)

Poburko D, Santo-Domingo J & Demaurex N. Dynamic regulation of the mitochondrial proton gradient during cytosolic calcium elevations. J. Biol. Chem. 286:11672-84 (2011)

*5) **Proton channels and the phagocytic oxidase.** We have identified voltage-gated proton channels and established their physiological role in phagocytic white blood cells.*

El Chemaly A, Jaquet V, Cambet Y, Caillon A, Cherpin O, Balafa A, Krause KH, Demaurex N. Discovery and validation of new Hv1 proton channel inhibitors with onco-therapeutic potential. Biochim Biophys Acta Mol Cell Res. (2023). DOI: 10.1016/j.bbamcr.2022.119415

El Chemaly A, Okochi Y, Sasaki M, Arnaudeau S, Okamura Y & Demaurex N. VSOP/Hv1 proton channels sustain calcium entry, neutrophil migration, and superoxide production by limiting cell depolarization and acidification, J. Exp. Med 207:129-39 (2010).

Bánfi B, Maturana A, Jaconi S, Arnaudeau S, Laforge T, Sinha B, Ligeti E, Demaurex N & Krause KH. A mammalian H+ channel, generated through alternative splicing of the NADPH oxidase homologue NOH-1. Science 287: 138-42 (2000).

Bánfi B, Schrenzel J, Nüße O, Lew DP, Ligeti E, Krause KH & Demaurex N. A novel H+ conductance in eosinophils: unique characteristics & absence in Chronic Granulomatous Disease. J. Exp. Med. 190: 183-194 (1999).

Demaurex N, Grinstein S, Jaconi ME, Schlegel W, Lew DP, & Krause KH. Proton currents in human granulocytes: regulation by plasma membrane potential and intracellular pH. J. Physiol. 466: 329-344 (1993)

Geneva, January 30th, 2023 Nicolas Demaurex