

## Carlos G. Dotti

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MD Medicine and Surgery, National  
University of Cordoba, Argentina 1979  
PhD Neuroscience, National University of  
Cordoba, Argentina 1985  
Postdoc Neurobiology, Albany Medical  
College, Albany N.Y. (USA). 1985-1988  
Postdoc Neuro-Cell Biology, EMBL  
Heidelberg 1988-1991



### Current Project Members

Staff Scientist: Annette Gärtner  
PhD student: Antonio Laranjeira  
Technical staff: Jarl Bastianen  
Administrative staff: Isabelle Lahousse

### Keywords

Neuronal polarity – brain aging – gene identification – cholesterol loss - MARCKS

### Science

Learning and memory decline with age. The same can be observed if cellular models of learning and memory are used, for long-term potentiation (LTP) and long-term depression (LTD), which represent two most established models of cognition. On the other hand, aging is not paralleled by neuronal loss, implying the existence of most strong survival mechanisms at the same time when synaptic function decays. It is unclear whether these two events, strong survival and reduced performance, are molecularly linked, interdependent.

We have recently demonstrated that during aging hippocampal neurons gradually but persistently lose cholesterol from the plasma membrane: in the mouse the decrease reaches 25%. The cholesterol loss is compensated by the increase in other lipids (i.e. sphingomyelin) resulting consequently in that the plasma membrane of old neurons is significantly different from that of young neurons, in composition, molecular organization and in function. In fact, one consequence of cholesterol loss/sphingomyelin gain with age is a strong ligand-independent activation of the receptor tyrosine kinase pathway TrkB, in turn important to give survival resistance to old neurons. We are now trying to elucidate to which extent this age-associated, cholesterol loss-mediated, survival robustness is, at least to a certain extent, responsible for the cognitive decay of the old. We have tested this hypothesis by manipulating the cholesterol content of the neuronal plasma membranes by various means, pharmacological and molecular, both in gain and loss-of-function paradigms and in different experimental systems, in vitro and in vivo. Provisional evidence indicates that age-associated cholesterol dys-homeostasis is a key determinant in the cognitive process, molecularly linked to the increased survival.

### Awards:

1985	Fogarty International Fellows, National Institute of Health (NIH), Bethesda, USA
1988	Alexander von Humboldt Stiftung, Bonn, Germany
2000	EMBO Member

## Selected Publications

Martin, M., Perga, S., Trovo, L., Rasola, A., Holm, P., Rantamäki, T., Harkany, T., Castrén, E., Chiara, F. and **Dotti, C.G.** (2008) Cholesterol loss enhances TrkB signaling in hippocampal neurons aging in vitro. *Mol. Biol. Cell* 19(5); 2101-2112.

Pollarolo, G., Schulz, J., Munck, S. and **Dotti C.G.** (2011). Cytokines remnants determine neuronal polarity in vivo. *Nature Neurosci.* 14, 1525-1533.

Ledesma, M.D., Martin, M.G. and **Dotti, C.G.** (2012). Lipid changes in the aged brain: effect on synaptic function and neuronal survival. *Progr. Lipid Research*, 51, 23-35. (*Review*)

Sodero, A., Vriens, J., Ghosh, D., Stegner, D., Brachet, A., Pallotto, M., Sassoe-Pognetto, M., Browsers, J.,F., Helms, J.B., Nieswandt, B., Voets, T. and **Dotti, C.G.** (2012). Cholesterol loss during glutamate-mediated excitotoxicity. *EMBO J.* 31, 1764-1773

Gaertner, A., Fornasiero, E.F., Munck, S., Vennekens, K., Seuntjens, E., Huttner, W.B., Valtorta, F. and **Dotti, C.G.** (2012). N-cadherin specifies first asymmetry in developing neurons. *EMBO J.* 31, 1893-2003.

Guix, F., Wahle, T., Vennekens, K., Senllinx, A., Chavez-Guiterrez, L., Ill-Raga., F., Ramos, E., Guardia-Laguarta, C., Lleó, A., Arimon, M., Berezovska, O., Muñoz, F.J., **Dotti, C.G.\***, and De Strooper, B. (2012). Modification of g-secretase by nitrosative stress links neuronal aging to sporadic Alzheimer's disease. *EMBO Molecular Medicine* 4(7). 660-73 *\*co-corresponding author.*

Cáceres A, Ye B, **Dotti CG.** (2012) Neuronal polarity: demarcation, growth and commitment. *Curr Opin Cell Biol.* 2012 Aug; 24(4):547-53. (*Review*)

Trovò. L., Ahmed, T., Buzzi, A., Callaerts-Vegh, Z., Bagni, C., Chua, M. VandenDriessche, T., D'Hooge, R., Balschum, D. and **Dotti, C.G.** (2013). Low hippocampal PI(4,5)P2 contributes to reduced cognition in old mice due to loss of MARCKs. *Nature Neurosci.* 16(4):449-55.

[All publications](#)