



**NEW FRONTIERS IN NEUROACANTHOCYTOSIS AND NEURODEGENERATION
WITH BRAIN IRON ACCUMULATION: FROM BENCHSIDE TO BEDSIDE**

**THE THIRD JOINT SYMPOSIUM ON NEUROACANTHOCYTOSIS
AND NEURODEGENERATION WITH BRAIN IRON ACCUMULATION**

October 30th - November 1st, 2014

La Palma Hotel - Stresa

Title	IN ChAc RED CELLS THE ABNORMALLY ACTIVATED LYN AFFECTS ANKYRIN MULTIPROTEIN COMPLEXES AND IS INHIBITED BY DASATINIB
Authors	Francesca Lupo ^{1*} , Elena Tibaldi ^{1°} , Anna Maria Brunati [°] , Alessandro Mattè*, Angela Siciliano*, Adrian Danek [^] , Ruth H Walker §, Andreas Hermann>, Lucia De Franceschi
	<p>* Department of Medicine, University of Verona, Italy; ° Department of Biochemistry, University of Padova, Italy; ^Department of Neurology, Ludwig-Maximilians-Universität, Munich, Germany; §Department of Neurology, James J Peters VAMC, Bronx, New York, and Mount Sinai School of Medicine, New York, USA; > Department of Neurology, Dresden University of Technology and German Centre for Neurodegenerative Disease (DZNE), Dresden, Germany.</p>
	<p>Chorea-acanthocytosis (ChAc) is a hereditary neurodegenerative disorder, one of the neuroacanthocytosis syndromes (NA). One of the hallmarks of NA is the presence of circulating acanthocytes, generation of which is still under investigation. Recently, we reported increased Tyrosine phosphorylation state of the red blood cell (RBC) membrane proteins from ChAc patients, related to abnormal activation of Lyn, an Src family kinase (SFKs) (Blood 118; 5652; 2011). In the context of international collaboration, we further characterized Lyn signaling pathway in RBC from ChAc patients. In ChAc RBCs, we found a weakness of ankyrin-based multiprotein complex bridging the membrane to the cytoskeleton, contributing to the generation of acanthocytes. We then evaluated the state of Lyn (active-inactive) in the cytoplasmic fraction from RBC of ChAc patients. In ChAc RBCs we found higher levels of Phospho- Lyn-396, corresponding to active Lyn, compared to controls. We then evaluated whether classical Lyn inhibitors such as PP2 or Dasatinib, a pharmacological Lyn inhibitor, might block Lyn in ChAc RBCs. We found that both PP2 (0.1 μM) or Dasatinib (0.1 μM) were able to efficiently inhibit Lyn in both ChAc and healthy RBCs. These data suggest that in ChAc (i) the abnormal activation of Lyn affects RBC membrane mechanical stability weakening both multiprotein complexes, bridging the membrane to the cytoskeleton; (ii) Lyn activity is inhibited by either PP2 or Dasatinib, suggesting Lyn as possible new therapeutic target in ChAc.</p>
	<p>This work was supported by NA advocacy and Telethon grant GP13005 and Erare-JTC 2012 (“EMINA2”)</p>
	<p>¹ These two Authors have equally contributed</p>

Name and Surname of first author: Francesca Lupo

Address: Department of Medicine, University of Verona, P.le L.Scuro, 10, 37134 Verona, Italy.

Tel: +39 0458128419

E-mail: francesca.lupo@univr.it