Santina Bruzzone

Associate professor

santina.bruzzone@unige.it
+39 010 353 8161
+39 010 353 8131

Education and training

2000
PhD in Biotechnology applied to Pharmacology and Cellular and Molecular Biotechnology applied to Biomedicine
The CD38/cyclic ADP-ribose system a topological paradox
University of Milan - Milan - IT

1996
Degree in Biology
Deplezione della glicoproteina di membrana CD38 e sua internalizzazione mediata da NAD+ nelle cellule B Namalwa - 110/110 e lode
University of Genova - Genova - IT

Academic experience

2016 - ONGOING
Associate Professor of Biochemistry
University of Genova - Genova - IT

2005 - 2016
Assistant Professor of Biochemistry
University of Genova - Genova - IT

2002 - 2005
Post-doctoral fellow
University of Genova - Genova - IT

2001
Post-doctoral fellow
University of Minnesota - Minneapolis MN - US

Language skills

English
Proficient

Research interests

1. NAD biology

I am interested in therapeutic approaches targeting NAD biosynthesis and NAD-degrading enzymes, such as SIRT6 and CD38. In addition to its role as a coenzyme, NAD is a signaling molecule, being the substrate of CD38 (with production of Ca2+-mobilizing second messengers), of sirtuins, and of PARPs. Both NAD-degrading enzymes and NAD biosynthesis have been widely investigated in cancer treatment. We contributed in this area, with studies focusing on the NAD-metabolizing enzymes CD38 and SIRT6, and on the NAD biosynthetic enzyme nicotinamide phosphoribosyltransferase (NAMPT). Namely, our main achievements can be summarized as follows:

1. **CD38**. Since my PhD and post-doctoral training at the University of Minnesota, I have always been interested in the role of NAD-derived, CD38-generated second messengers in the pathophysiology of different disorders, including cancer (reviewed in De Flora et al Ann NY Acad Sci, 2004). This interest culminated in a collaboration with Prof Deaglio (University of Torino), demonstrating, in an in vivo animal model, that targeting the enzymatic activities of CD38 is a promising strategy in CLL (Vaisitti et al. Leukemia 2015).
2. **SIRT6**. In collaboration with Prof Nencioni (DIMI, University of Genova) and Dr Del Rio (CNR, Bologna), we identified the first potent and selective SIRT6 inhibitors (Parenti et al J Med Chem 2014; Sociali et al Eur J Med Chem 2015; Damonte et al Bioorg Med Chem 2017). These compounds are predicted to be applicable as chemosensitizers in the cancer types in which SIRT6 seems to act as an oncogene (i.e. skin and prostate cancer). In addition, we collaborated with Dr Cea in defining SIRT6 role in acute myeloid leukemia (Cagnetta et al Haematologica 2018). Finally, we demonstrated that SIRT6 inhibitors ameliorated glycemia and lipid profile in a murine model of type 2 diabetes (Sociali et al FASEB J 2017).
3. **NAD synthesis**. Targeting NAD production is considered a promising strategy in oncology. Most of the efforts of the scientific community have been directed to the discovery of NAMPT inhibitors. However, there is now a general agreement that targeting NAMPT is unlikely to be sufficient per se. In collaboration with Prof Nencioni, Dr Cea and Dr Zoppoli (DIMI, University of Genova), we identified successful combinations of NAMPT inhibitors with other agents for treating leukemia (Zoppoli et al Exp Hematol 2010; Cea et al PLoS One 2011; Cagnetta et al Clin Cancer Res 2015). In addition, we collaborated to the identification of extracellular NAMPT as a pro-tumorigenic cytokine in breast cancer (Soncini et al J Biol Chem 2015). More recently, we showed that combining NAMPT and CD73 inhibitors might represent another therapeutic approach for ovarian cancer and potentially for other CD73-overexpressing types of cancer

(Sociali et al Oncotarget 2016; Grozio et al J Biol Chem 2013). Finally, my team collaborated with Prof Nencioni's group in defining the role of NAPRT in cancer (Piacente et al Cancer Res 2017).

1. The purinergic receptor/channel P2X7

In collaboration with Prof. Schenone's group at the DINOGMI, University of Genova, we demonstrated that an increased intracellular calcium mediated by the purinoceptor **P2X7 causes functional derangement in Schwann cells (SC) from rats with Charcot-Marie-Tooth 1A** (CMT1A) neuropathy (Nobbio et al J Biol Chem 2009). We also identified a new P2X7 antagonist (named P18), which antagonizes the ATP-induced opening of P2X7 (Bruzzone et al J Biol Chem 2010; Basile et al PNAS 2005). We demonstrated that P18 is able to restore normal levels of [Ca2+]i in CMT1A SC (Nobbio et al J Cell Biochem 2014). In collaboration with Prof Sereda (Max-Planck-Institute for Experimental Medicine, Göttingen, Germany), we demonstrated that pharmacological inhibition of the P2X7 receptor is well tolerated in CMT1A rats and represents a proof-of-principle that antagonizing this pathway may correct the molecular derangements and improve the clinical phenotype in the CMT1A neuropathy (Sociali et al Neurobiol Dis 2016).
Currently, we are collaborating with Dr Bruno (Gaslini Institute, Genova) in a project regarding the role of P2X7 in muscle dystrophy.

1. Abscisic acid in humans.

In collaboration with Prof Zocchi (DIMES, University of Genova) we have been investigating the role of the plant hormone abscisic acid (ABA) in lower Metazoa and in mammalian cells. We delineated the ABA-triggered signaling pathway in mammalian cells (*Bruzzone et al PNAS 2007; Sturla et al J Biol Chem 2009*). Next, our interest shifted to the role of ABA in glucose homeostasis maintenance: we demonstrated that ABA stimulates glucose-dependent and –independent release of insulin from human pancreatic islets and that ABA is released by these cells when exposed to glucose (Bruzzone et al J Biol Chem 2008). Plasma ABA increases after oral glucose load in normal subjects (Bruzzone et al FASEB 2012) but not in subjects with type 2 diabetes and in women with gestational diabetes (Ameri et al, Plos One 2015). Impairment of the response of plasma ABA to hyperglycemia in diabetes suggests a critical role for ABA in the maintenance of glucose tolerance. Indeed, besides stimulating insulin release, ABA exerts other effects impacting on glucose homeostasis: ABA increases glucose uptake by myoblasts and adipocytes, by increasing the plasmamembrane translocation of the glucose transporter GLUT4 (Bruzzone et al FASEB 2012; Sturla et al BBA 2017) and stimulates the release of GLP-1 by enteroendocrine L-cells (Bruzzone et al, Plos One 2015). Oral administration of ABA induced an increase in plasma GLP-1 levels. Intriguingly, GLP-1 was demonstrated to evoke ABA release from human pancreatic islets. These results suggest presence of a positive feed-back mechanism between ABA and GLP-1, possibly relevant to glycemia regulation. We are currently

interested in the interplay between GLP-1, ABA and insulin in different organs and cell types.