



## Prof. Stefano Piccolo

### Full Professor of Molecular Biology



#### **Most important awards, prizes and academies**

*Honors/Awards:* 2003: A. Minich Award from Istituto Veneto Scienze, Lettere ed Arti (Venice); 2005: International Swissbridge Award (Zurich); 2007: Chiara D'Onofrio Award (top Biomedical Award for Italian scientists under 40); 2011: International Debiopharm Award (Lausanne); 2012: International Tartufari award from Accademia Nazionale Lincei (Rome); 2012: Presidential Venosta Award (main cancer award in Italy) from Fondazione Italiana Ricerca sul Cancro (Rome); 2015: ERC Advanced Grant; 2017: Choh Hao Li Memorial Lectures award (UC Berkeley). *Institutional responsibilities:* 2015-2019: Member of AIRC Scientific Advisory Board; 2004-2008: AIRC Grant review panellist. *Commissions of trust:* 2013-2019 EMBL Scientific Advisory board (SAC, member); 2012-2014 ERC starting and consolidator award (member); 2010-present Pezcoller Foundation Symposia Scientific Board; 2012 and 2017 Pezcoller-AACR Award Committee. Membership of scientific societies: 2007- EMBO member; 2014- Accademia dei Lincei, Rome (Member); Member of AACR, SIBBM; 2014- International Society of Differentiation, Board of Directors.

#### **Summary of scientific research**

Our pathfinding contribution has been the discovery that cells convert the mechanical signals that surround them into the activity of two potent transcription factors, YAP and TAZ. This

“mechanotransduction” cascade is now envisioned as an overarching cellular signaling conduit by which cells perceive themselves – their own shape, adhesion and microenvironmental context – and respond to these physical cues by tuning their behavior according to tissue needs (Dupont et al., *Nature* 2011; Aragona et al., *Cell* 2013; Halder et al., *Nat Rev MCB* 2012; Totaro et al., *Nat Comm* 2017; Chang et al., 2018, *Nature* 2018). These mechanisms of cellular “social behavior” are corrupted in cancer, where indeed altered mechanical signals drive aberrant YAP/TAZ activation. We indeed showed that YAP/TAZ are required for tumorigenesis, promoting phenotypic plasticity in cancer cells, and expansion of tumor cells endowed with stemness, proliferative and chemoresistance attributes (Panciera et al., *Nature Materials* 2020; Cordenonsi et al., *Cell* 2011; Azzolin et al., *Cell* 2012; Azzolin et al., *Cell* 2014; Zanconato et al., *Nat Cell Biol* 2015; Zanconato et al., *Nat Medicine* 2018; Chang et al., *Nature* 2018).

In normal cells, we pioneered the role of YAP/TAZ as cell reprogramming factors: in different tissues, activation of YAP/TAZ turns differentiated cells into their corresponding somatic stem cells (Panciera et al., *Cell Stem Cell* 2016). This form of cell plasticity is exploited for tissue regeneration after damage and for 3D outgrowth of minitissues (“organoids”) (Yui et al., *Cell Stem Cell* 2018; Azzolin et al., *Cell* 2014).

We also added new dimensions to such biomechanical regulation of cell behavior, revealing interactions between mechanical signals and other signals and cellular factors (Azzolin et al., *Cell* 2012; Azzolin et al., *Cell* 2014; Nowell et al., *Nat Cell Biol.* 2015; Totaro et al., *Nat Comm* 2017; Chang et al., *Nature* 2018). In a different research line, we have identified novel metastasis inducing and suppressing mechanisms (Adorno et al., *Cell* 2009; Martello et al., *Cell* 2010; Montagner et al., *Nature* 2012).

## Main publications

2020 Panciera T, Citron A, Di Biagio D, Battilana G, Gandin A, Giulitti S, Forcato M, Bicciato S, Panzetta V, Fusco S, Azzolin L, Totaro A, Dei Tos AP, Fassan M, Vindigni V, Bassetto F, Rosato A, Brusatin G, Cordenonsi M, Piccolo S. Reprogramming normal cells into tumour precursors requires ECM stiffness and oncogene-mediated changes of cell mechanical properties. *Nature Materials.* 19, 797-806; 2019 Totaro A, Zhuang Q, Panciera T, Battilana G, Azzolin L, Brumana G, Gandin A, Brusatin G, Cordenonsi M, Piccolo S. Cell phenotypic plasticity requires autophagic flux driven by YAP/TAZ mechanotransduction. *Proc Natl Acad Sci U S A.* 116, 17848-17857; 2018 Chang L, Azzolin L, Di Biagio D, Zanconato F, Battilana G, Lucon Xiccato R, Aragona M, Giulitti S, Panciera T, Gandin A, Sigismondo G, Krijgsveld J, Fassan M, Brusatin G, Cordenonsi M, Piccolo S. The SWI/SNF complex is a mechanoregulated inhibitor of YAP and TAZ. *Nature.* 563, 265-269; 2018 Zanconato F, Battilana G, Forcato M, Filippi L, Azzolin L, Manfrin A, Quaranta E, Di Biagio D, Sigismondo G, Guzzardo V, Lejeune P, Haendler B, Krijgsveld J, Fassan M, Bicciato S, Cordenonsi M, Piccolo S. Transcriptional addiction in cancer cells is mediated by YAP/TAZ through BRD4. *Nature Medicine.* 24, 1599-1610; 2018 Yui S, Azzolin L, Maimets M, Pedersen MT, Fordham RP, Hansen SL, Larsen HL, Guiu J, Alves MRP, Rundsten CF, Johansen JV, Li Y, Madsen CD, Nakamura T, Watanabe M, Nielsen OH, Schweiger PJ, Piccolo S, Jensen KB.

YAP/TAZ-Dependent Reprogramming of Colonic Epithelium Links ECM Remodeling to Tissue Regeneration. *Cell Stem Cell*. 22, 35-49.e7; 2017 Totaro A, Castellan M, Battilana G, Zanconato F, Azzolin L, Giulitti S, Cordenonsi M, Piccolo S. YAP/TAZ link cell mechanics to Notch signalling to control epidermal stem cell fate. *Nature Communications*. 8, 15206; 2016 Panciera T, Azzolin L, Fujimura A, Di Biagio D, Frasson C, Bresolin S, Soligo S, Basso G, Bicciato S, Rosato A, Cordenonsi M, Piccolo S. Induction of Expandable Tissue-Specific Stem/Progenitor Cells through Transient Expression of YAP/TAZ. *Cell Stem Cell*. 19, 725-737; 2016 Nowell CS, Odermatt PD, Azzolin L, Hohnel S, Wagner EF, Fantner GE, Lutolf MP, Barrandon Y, Piccolo S, Radtke F. Chronic inflammation imposes aberrant cell fate in regenerating epithelia through mechanotransduction. *Nature Cell Biology*. 18, 168-180; 2015 Zanconato F., Forcato M., Battilana G., Azzolin L., Quaranta E., Bodega B., Rosato A., Bicciato S., Cordenonsi M. and Piccolo S. [Genome-wide association between YAP/TAZ/TEAD and AP-1 at enhancers drives oncogenic growth](#). *Nature Cell Biology*. 9, 1218-27; 2014 Azzolin L, Panciera T, Soligo S, Enzo E, Bicciato S, Dupont S, Bresolin S, Frasson C, Basso G, Guzzardo V, Fassina A, Cordenonsi M, Piccolo S. [YAP/TAZ Incorporation in the  \$\beta\$ -Catenin Destruction Complex Orchestrates the Wnt Response](#). *Cell*. 158, 157-70; 2014 Piccolo S. Twists of fate: cells as mechanical machines. *Scientific American* 311, 74-81; 2013 Aragona M, Panciera T, Manfrin A, Giulitti S, Michielin F, Elvassore N, Dupont S and Piccolo S. A mechanical checkpoint controls multicellular growth through YAP/TAZ regulation by actin-processing factors. *Cell* 154, 1047-59; 2012 Montagner M, Enzo E, Forcato M, Zanconato F, Parenti A, Rampazzo E, Basso G, Leo G, Rosato A, Bicciato S, Cordenonsi M and Piccolo S. Sharp1 suppresses breast cancer metastasis by promoting degradation of HIFs/hypoxia-inducible factors. *Nature* 487, 380-4; 2012 Azzolin L, Zanconato F, Bresolin S, Forcato M, Basso G, Bicciato S, Cordenonsi M, Cordenonsi M, and Piccolo S. Role of TAZ in Wnt signaling. *Cell* 7, 1443-56; 2011 Cordenonsi M, Zanconato F, Azzolin L, Forcato M, Rosato A, Frasson C, Inui M, Montagner M., Parenti A, Poletti A, Daidone MG, Dupont S, Basso G, Bicciato S, and Piccolo S. The Hippo Transducer TAZ Confers Cancer Stem Cell-related Traits on Breast Cancer Cells. *Cell* 147, 759-72; 2011 Dupont S, Morsut L, Aragona M, Enzo E, Giulitti S, Zanconato F, Le Digabel J, Forcato M, Elvassore N and Piccolo S. Role of YAP/TAZ in mechanotransduction. *Nature* 474, 179-183; 2011 Inui M, Manfrin A, Mamidi A, Martello G, Morsut L, Soligo S, Enzo E, Moro S, Polo S, Dupont S, Cordenonsi M, and Piccolo S. USP15 is a deubiquitylating enzyme for receptor-activated SMADs. *Nature Cell Biology* 13, 1368-75; 2010 Martello G, Rosato A, Ferrari F, Manfrin A, Cordenonsi M, Dupont S, Enzo E, Guzzardo V, Rondina M, Spruce T, Parenti AR, Daidone MG, Bicciato S and Piccolo S. A microRNA targeting Dicer for metastasis control. *Cell* 141, 1195-1207; 2009 Adorno M, Cordenonsi M, Montagner M, Dupont S, Wong C, Hann B, Solari A, Parenti R, Rosato A, Bicciato S, Balmain A and Piccolo S. A mutant-p53/Smad complex opposes p63 to empower TGF-beta induced metastasis. *Cell* 137, 87-98; 2009 Dupont S, Mamidi A, Cordenonsi M, Montagner M, Zacchigna L, Adorno M, Martello M, Stinchfield MJ, Soligo S, Morsut L, Inui M, Moro S, Modena M, Argenton F, Newfield S and Piccolo S. FAM/USP9x, a deubiquitinating enzyme essential for TGF-beta signaling controls Smad4 monoubiquitination. *Cell* 136, 123-135; 2007 Martello G, Zacchigna L, Inui M, Montagner M, Adorno M, Mamidi A, Morsut L, Soligo S, Tran U, Dupont S,

Cordenonsi M, Wessely O and Piccolo S. MicroRNA control of Nodal signalling. *Nature* 449,183-8; 2007 Cordenonsi M, Montagner M, Adorno M, Zacchigna L, Martello G, Mamidi A, Soligo S, Dupont S, and Piccolo S. Integration of TGF- $\beta$  and Ras/MAPK signaling through p53 phosphorylation. *Science* 315, 840-3; 2006 Zacchigna, L., et al., Piccolo\*, S. and G.M. Bressan\*. Emilin1, a cysteine-rich glycoprotein of elastic fibers, is required for blood pressure homeostasis by regulating TGF-b maturation (2006). *Cell* 124, 929-42 # co-corresponding authors; 2005 Dupont, S., Zacchigna, L., Cordenonsi, M., Soligo, S., Adorno, M., Rugge, M., and Piccolo, S. Germ-layer specification and control of cell growth by Ectodermin, a Smad4 ubiquitin ligase. *Cell* 121, 87-99; 2003 Cordenonsi, M., Dupont, S., Maretto, S., Insinga, A., Imbriano, C., and Piccolo, S. Links between tumor suppressors: p53 is required for TGF-b gene responses by cooperating with Smads. *Cell* 113, 301-314; 2003 Maretto, S., Cordenonsi, M., Dupont, S., Braghetta, P., Broccoli, V., Hassan, A. B., Volpin, D., Bressan, G. M., and Piccolo, S. Mapping Wnt/ $\beta$ -catenin signaling during mouse development and in colorectal tumors. *Proc Natl Acad Sci U S A* 100, 3299-3304. *Main reviews*: 2019 Zanonato F, Cordenonsi M, Piccolo S. YAP and TAZ: a signalling hub of the tumour microenvironment. *Nature Reviews in Cancer*. (review) 19, 454-464; 2018 Brusatin G, Panciera T, Gandin A, Citron A, Piccolo S. Biomaterials and engineered microenvironments to control YAP/TAZ-dependent cell behaviour. *Nature Materials* (review) 17, 1063-1075; 2018 Totaro A, Panciera T, Piccolo S. YAP/TAZ upstream signals and downstream responses. *Nature Cell Biology* (review) 20, 888-899; 2017 Panciera T, Azzolin L, Cordenonsi M, Piccolo S. Mechanobiology of YAP and TAZ in physiology and disease. *Nat Rev Mol Cell Biol.* (review) 18, 758-770; 2016 Zanonato F., Cordenonsi M. and Piccolo S. YAP/TAZ at the roots of cancer. *Cancer Cell* (review) 29, 783-803.