STEFANO PICCOLO *Curriculum Vitae*

PERSONAL INFORMATION

Family name, First name: Piccolo, Stefano
Nationality: Italian
Date of birth:
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EDUCATION

1995 - 1999: HHMI post-doctoral fellow with Prof. Eddy De Robertis, University of California, Dept. of Biological Chemistry
1995 PhD in Biochemistry and Pathology of the Extracellular Matrix; University of Padua, School of Medicine, Padua, Italy.
1991 Master in Biological Sciences, University of Padua, Italy (score: *magna cum laude*).

CURRENT POSITION

Full Professor of Molecular Biology, University of Padua School of Medicine

AWARDS

1999: International BIOTECH Award (Milan)
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, from Fondazione Italiana Ricerca sul Cancro (Rome)
2017: Choh Hao Li Memorial Lectures award (UC Berkeley)

INSTITUTIONAL RESPONSIBILITIES

2015 - present Member of AIRC Scientific Advisory Board
2012 - present Director PhD program in Molecular Medicine, University of Padua
2004 - present AIRC Grant (2004-2008) and Fellowships (2011-present) review panellist

COMMISSIONS OF TRUST

2013 - present EMBL Scientific Advisory Council (member)
2012 - 2014 ERC starting and consolidator award (member)
Pezcoller Foundation Scientific Board (2010-) and Pezcoller-AACR Award Committee

MEMBERSHIPS OF SCIENTIFIC SOCIETIES

2007 - EMBO member
2014 - Accademia dei Lincei, Rome (Member)
Member of AACR, SIBBM

OTHER ACTIVITIES

- *Ad hoc* reviewer for career promotions and awards in Italy and for leading research institutions worldwide.
- Member of the Editorial Board of EMBO Report, Cell Death and Differentiation, Disease Models and Mechanisms, Molecular and Cellular Oncology, Cell Stress
- Reviewer activity: Regularly for Cell, Cancer Cell, Nature, Nature Cell Biology, Nature Medicine, Nature Comm., EMBOJ, EMBO Report, Journal of Cell Biology, Molecular Cell. Occasionally for Cancer Research, Development, Nature Genetics, Nature reviews journals, Current Biology.

TRACK-RECORD AND INVITATIONS AT INTERNATIONAL CONFERENCES

I started my lab in 1999. Throughout my career, I have pursued research lines that I considered innovative and used multidisciplinary approaches to push our research efforts significantly beyond the state of the art. I contributed as corresponding author to 10 papers in Cell, 3 in Nature, 2 in Nature Cell Biology and others in Science, Cell Stem Cell, Cancer Cell, Nat. Comm. and Nature Genetics; plus Reviews, and commentaries in these and other leading journals. For 2018, we are at advanced stages for papers in Nature, Nature Medicine and Nature Cell Biology.

In the last 5 years I participated as invited speaker, keynote lecturer or organizer to more than 50 international conferences, including some of the most prestigious symposia in the fields of stem cells, cancer and mechanobiology.

PATENTS

2017: "Compounds for somatic stem cell fate control U.S. No. 62,484,566,
2015: “Methods for generating somatic stem cells” PCT/EP2015/070305
2011: "Composition for use in treating or preventing cancer”, PCT/EP2010/058495
2010: "Prognosis of Breast Cancer Patients by monitoring two genes” PCT/EP2009/050643
2007: "TGF-beta modulators and use thereof" PCT/IB2007/000233

MAIN ACHIEVEMENTS (only papers with SP as corresponding author are listed below)

1) Cellular mechanotransduction as an overarching regulator of cell behavior through YAP/TAZ nuclear factors. Cell fate is potently influenced by mechanical forces, defining the cell's "social" behavior and organization within tissues. How this occurred remained a mystery for decades. We pioneered the discovery of a central mechanosensitive signaling cascade: cells translate information from the physicality of their microenvironment into activity of two potent transcriptional regulators, YAP and TAZ (Dupont et al., *Nature* 2011; Aragona et al., *Cell* 2013; Halder et al., Nat Rev MCB 2012; Totaro et al., Nat Comm 2017). Thanks to the work of many other investigators, this is now a "universal" pathway, with YAP/TAZ being downstream of multiple types of mechanical inputs (e.g., cell shape and extracellular matrix rigidity, adhesion, shear stress, substrate topology and tissue geometry and others) (Panciera et al., Nat Rev. MCB 2017). Coupled with the potent biological properties of YAP/TAZ (to which we also contributed, see below), this is impacting on different fields (from cell and developmental biology, to stem cells, tumor biology, signal transduction and biomaterials). Importantly, YAP/TAZ mechanotransduction is shedding new light on our understanding of how aberrant cell mechanics contributes to the pathogenesis of multiple diseases, such as atherosclerosis, fibrosis, hypertension, inflammation, muscular dystrophy and cancer (Zanconato et al., Cancer Cell 2016).

2) YAP/TAZ as reprogramming factors: role in de novo generation of somatic stem cells, tissue regeneration and organoids. We recently discovered that activation of YAP/TAZ turns differentiated cells of different types into their corresponding somatic stem cells. Namely, YAP or TAZ imbue cell fate plasticity and stemness but respect tissue barriers and lineage restrictions, as such establishing a new reprogramming paradigm (Panciera et al., Cell Stem Cell 2016). In particular, YAP/TAZ causes regression to a fetal-like cell state of a given organ, different from adult SCs, that in turn generates a progeny of adult SCs; YAP/TAZ are essential for tissue regeneration after damage, where this form of plasticity is in fact exploited in vivo (Yui and Azzolin, Cell Stem Cell 2017), and for 3D outgrowth of minitissues (or "organoids") ex vivo. YAP/TAZ inactivation is inconsequential for adult SCs and adult tissue homeostasis, making YAP/TAZ ideal target of cancer therapy.

3) New dimensions to YAP/TAZ biology and regulation. YAP/TAZ are currently at the centerpiece of intense investigations in the cancer field, given their essential roles in the development of multiple solid tumors (Piccolo et al., Phys. Rev, 2015; Zanconato et al, Cancer Cell 2016), to which we contributed by demonstrating the essential role of YAP/TAZ for breast cancer and breast cancer metastasis, intestinal transformation and skin tumorigenesis (Cordenonsi et al.

Cell 2011; Zanconato et al., Nat Cell Biol 2015; Azzolin et al., Cell 2014). Prior to our discovery of YAP/TAZ mechanotransduction, the only known regulation of YAP/TAZ was a *negative* one (and thus undruggable), that is, phosphorylation and inhibition by LATS1/2, one of the two kinases of the Hippo pathway. Our work on the YAP/TAZ biomechanical regulation opened unexpected new dimensions, revealing that YAP/TAZ absolutely require *positive* regulation by mechanical inputs, as such indicating unprecedented routes for YAP/TAZ inhibition by using small molecules. YAP/TAZ mechanotransduction also underlies cancer chemoresistance (Zanconato, EMBO J, 2015). We also pioneered how YAP/TAZ operates at the genome-wide level, discovering by ChIPseq and HiC the epigenetic and transcriptional mechanisms and downstream targets, also discovering a massive cooperation between AP1 (JUN/FOS) and YAP/TAZ (Zanconato et al., Nat. Cell Biol., 2015).

For proper control of cell behavior, there must exist reciprocal interactions between mechanical and chemical (i.e. growth factors' mediated) signals. YAP/TAZ represent an ideal hub for such integration. We recently discovered that in presence of a competent mechanical environment, YAP/TAZ mediate some of the effects of Wnt signaling (Azzolin et al., Cell 2012 and Cell 2014; Aragona et al., Cell 2013).

4) Role of YAP/TAZ in cancer: inducers of Cancer Stem Cells and malignancy. YAP/TAZ are important determinants of cancer; we contributed to this notion by using functional assays, mouse models and signatures of YAP/TAZ activity for human tumors (Cordenonsi et al., Cell 2011; Azzolin et al., Cell 2012; Azzolin et al., Cell 2014; Zanconato et al., Nat. Cell Biol., 2015). An original concept that we pioneered in this area is that YAP/TAZ are so pervasively activated in malignancies because they induce traits typically of cancer stem cells; this represented the first demonstration that YAP/TAZ incite the ability of cancer cells to remain undifferentiated, self-renew, seed new tumors at high efficiency, spread metastasis and resist to chemotherapy (Cordenonsi et al., Cell 2011). Importantly, YAP/TAZ expression is not just expanding pre-existing cancer stem cells; rather, it converts more differentiated, non-stem tumor cells into cancer stem cell-like cells (Cordenonsi et al., Cell 2011).

5) Identification of novel metastasis inducing and suppressing mechanisms. We pioneered the notion that p63, a p53-related transcription factor, acts as bona fide "metastasis suppressor" gene in breast cancer, whose activity is opposed by mutant-p53, for which we provided for the first time direct evidence as metastasis-inducer (Adorno et al., Cell 2009). We further expanded on genes and mechanisms of metastasis suppression by the identification and function of the anti-metastatic functions of p63 target genes, such as Dicer and Sharp1 (Martello et al., Cell 2010; Montagner et al., Nature 2012).

Other prior achievements (not outlined due to space constraints) is work described in: Cordenonsi et al., Cell 2003; Cordenonsi et al., Science 2007; Zacchigna et al., Cell 2008; Inui et al., Nature Cell Biol 2011.