Initial research by Pier Giuseppe Pelicci’s research group demonstrated that the p66Shc adaptor protein controlled oxidative stress response and life span in mammals (Migliaccio et al., 1999; Nature 402: 309-113.). Hence, our early work showed that p66Shc regulates apoptosis and permanent embryo arrest during early mammalian development. Surprisingly, p66Shc expression is increased at the blastocyst stage of preimplantation development, without an associated increase in cell death. With our recently published and unpublished data I will discuss the novel roles for p66Shc in establishing pluripotent state and regulating cell fate decisions.