LSU HealthNewOrleans School of Medicine

*Neuroscience Center of Excellence*

# Chancellor's Award Lecture

*in Neuroscience*

## Dr. Gerry Melino


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**12:00 p.m.**
**Friday**
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**8th Floor**
**Neuroscience Center of Excellence Conference Room**

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## p73 and p63, the Ancestral Members of the p53 Family, in Neuroscience and Senescence

In the last ten years, p63 and p73 have been identified as the ancestral members of the p53 family. Despite the high sequence and structural similarity, the mouse knockouts revealed a crucial role in neural development for p73 and in epidermal formation for p63. We identified several transcriptional targets, the mechanisms of regulation of cell death, and the p63 isoform involved in epithelial development. Both genes are involved in female infertility and maternal reproduction (AJ Levine, *Nature Rev* MCB 2011) as well as in cancer formation (G Melino, *CDD* 2011; P Tucci *PNAS-USA* 2012), although with distinct mechanisms. TAp73 knockout mice (TW Mak, *G&D* 2008) show high tumor incidence with hippocampal dysegensis (M Agostini, *PNAS-USA* 2012). Conversely, ΔNp73 knockout mice (TW Mak, *G&D* 2010) show a very low incidence of cancer, with sign of moderate neurodegeneration with a significant loss of cellularity in the cortex. This indicate a distinct role for TAp73 and ΔNp73. p73 and p63 steady state protein levels are kept low under normal physiological conditions through post-translational modifications (JG Gong, *Nature* 1999) or degradation by the 26S proteasome, mediated by the HECT-containing E3 ubiquitin ligase ITCH (M Rossi, *EmboJ* 2005), FBXO45 (A Peschiaroli, *Oncogene* 2009), antizyme pathway (I Dulloo, *PNAS-USA* 2010) and PIR (BS Sayan, *PNAS-USA* 2010). We developed an ELISA high throughput screening for ITCH auto-ubiquitylation, resulting in several positive compounds that are able to modulate chemosensitivity at 10 μM concentration. These compounds could be offer novel therapeutic targets.

More recently, we described the involvement of p73 in senescence and metabolism. TAp73-null mice show a significant premature spontaneous aging phenotype at 14 months of age: alopecia, epidermal thinning, reduced subucutaneous fat, increased visceral fat TAp73, osteoporosis with scoliosis. This indicates that TAp73 protects against aging by regulating mitochondrial activity and preventing ROS accumulation. Indeed, both *in vivo* and *in vivo* TAp73-null mice show unbalanced mitochondrial redox defences, at least in part mediated by a direct transcriptional regulation of Cox4i1 (A Rufini, *G&D* 2012). TAp73 is also able to drive the expression of glutaminase type 2 (GLS2), acting on specific binding sites present on its promoter, and regulate the synthesis of serine. In agreement with these *in vitro* data, TAp73-null cells show clear metabolic defects in the glutamine/serine pathway affecting GSH and redox balance. In keeping, we show a role for TAp73 in the regulation of metabolic pathways.