

TARGETING β 2-ADRENERGIC RECEPTORS as a NEW STRATEGY for von HIPPEL-LINDAU DISEASE



Cuesta AM¹, Albiñana V¹, I de Rojas-P¹, Gallardo-Vara E¹, Recio-Poveda L¹, Villar Gómez de Las Heras K², Aguirre DT³, and Botella LM¹.

¹Centro de Investigaciones Biológicas Margarita Salas-CSIC. Madrid, Spain.

²SSCC del Servicio de Salud de Castilla-La Mancha (SESCAM). Toledo, Spain.

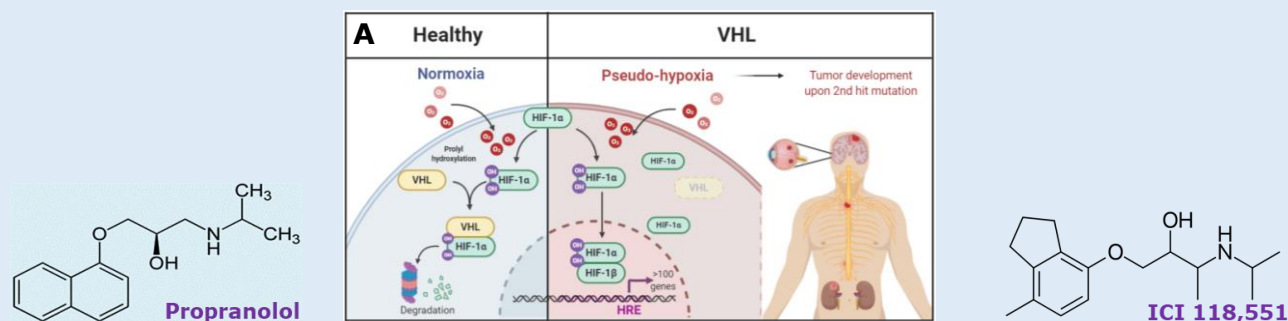
³Hospital Universitario Fundación Jiménez Díaz. Madrid, Spain.

Lab



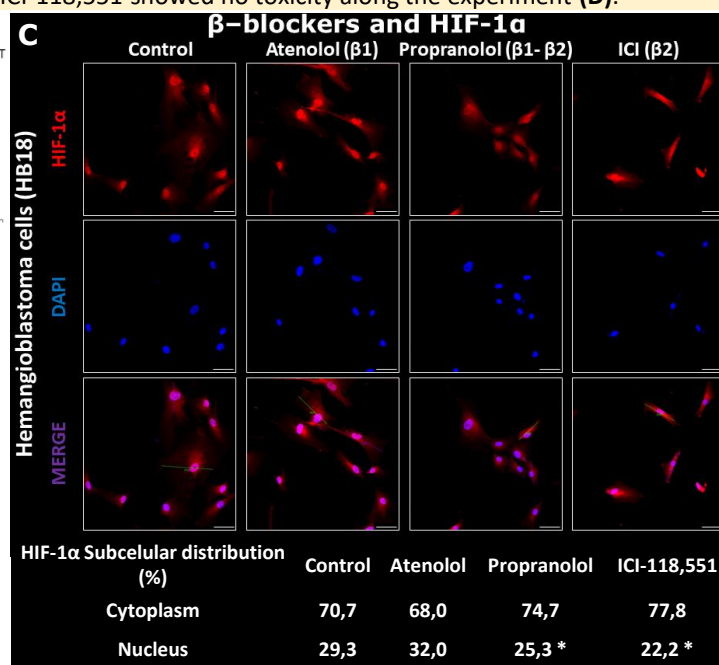
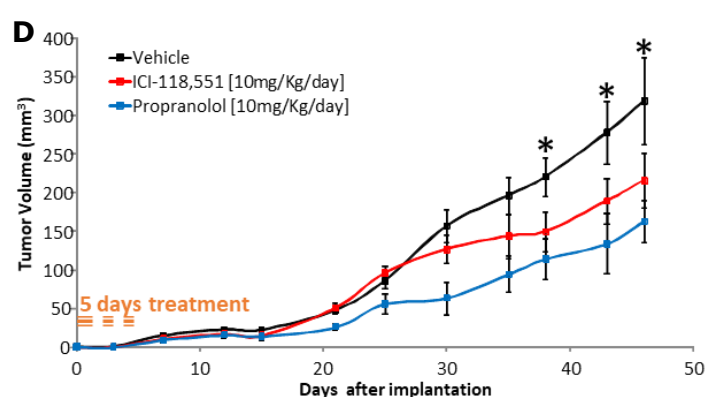
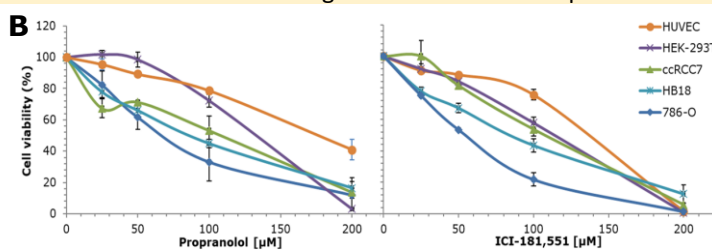
Von Hippel-Lindau (VHL) disease (A). The VHL protein belongs to the Ubiquitin ligase complex and regulates the proteolytic degradation of HIF1 α and HIF2 α . In VHL disease, the gene is mutated and therefore, the protein is misfolded or not expressed. In regular levels of oxygen (normoxia) HIFs are hydroxylated by PHD proteins and thus, recognized by VHL, being marked for degradation. In VHL disease, the consequence is similar to what happens in hypoxia (low oxygen levels): HIFs are not degraded and remain into the cell, triggering the expression of their target genes involved in processes such as angiogenesis, migration or proliferation. The main clinical manifestations are Central Nervous System (CNS) and retinal Hemangioblastomas (HB), clear cell renal carcinoma (ccRCC) or pheochromocytomas.

THIS HAPPENS NEITHER IN ALL THE CELLS NOR AT THE SAME TIME, BUT ALONG THE LIFE SPAN OF THE VHL PATIENT



Propranolol and ICI-118,551 have shown *in vitro* and *in vivo* therapeutical properties:

- in vitro* decrease on cell viability by triggering apoptosis after 72 hours treatment in CNS-HBs and ccRCC primary cultures and in 786-O ccRCC cell line, but not in renal HEK-293T and HUVEC cell lines (B);
- in vitro* impairment of the nuclear internalization of HIF-1 α in CNS-HBs, reducing significantly the activation of HIF-target genes and therefore, halting the tumor-related angiogenic process (C); and
- in vivo* antitumor therapeutic benefits: a 5 days systemic treatment reduced the tumor growth of a 786-O (10⁶ cells/mouse) subcutaneous xenograft on NSG mice. Propranolol and ICI-118,551 showed no toxicity along the experiment (D).



Propranolol, as Orphan Drug, and ICI-118,551, as potential future drug, are successful examples of the collaborative efforts between the VHL Spanish Alliance patients, clinicians, and CSIC researchers.

We demonstrate, for the first time, the therapeutic properties of targeting the β 2-receptors (using Propranolol or ICI-118,551) in VHL-derived CNS-HB and ccRCC primary cultures, the main life threat to patients, with surgery being the only proven efficient therapy.

Thus, ICI-118,551 has been licensed for VHL disease treatment and becomes a promising drug for VHL patients and potentially other HIF-related diseases.