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Von Hippel-Lindau disease (VHL) research in Spain has a notably translational character with direct networking between clinicians, VHL Spanish Alliance patients, and CSIC researchers. Propranolol, an antihypertensive, non-specific β-blocker, was re-discovered as a cure for Infantile Hemangioma and, later, different publications showed that Propranolol has antiangiogenic and proapoptotic properties. Different in vitro assays using propranolol in VHL primary cultures demonstrated that Propranolol triggered apoptosis in these cells. Moreover, Propranolol reduced the levels of Hypoxia Inducible Factor (HIF), constitutively expressed in VHL-derived tumors due to the lack of pVHL protein targeting HIF to proteasomal degradation under normoxia. A reduction of HIF led do downregulation of HIF targets, remarkably, VEGF (Vascular Endothelial Growth Factor), EPO (Erythropoietin), or SDX2. In vitro results and the known safety profile of Propranolol, allowed to organize a Phase III Clinical Trial (EudraCT Number: 2014-003671-30) evaluate the therapeutic effect and safety of Propranolol on 7 VHL patients suffering from retinal hemangioblastomas with no therapeutic option. Patients were treated with 120 mg/day Propranolol for a year. Retinal hemangioblastomas and VEGF plasma levels were followed-up along the trial. The results of the clinical trial showed a stop in the retinal hemangioblastoma growth, and no new tumors arose. In addition, 2 patients had a significant reduction of eye exudates detectable before the clinical trial and a significant reduction of the VEGF plasma levels was detected. Due to in vitro and in vivo results, Propranolol was designated by EMA as orphan drug for VHL treatment (EU/3/17/1841).

Propranolol shows properties as therapeutic drug for retinal hemangioblastomas and capabilities for CNS hemangioblastomas, and should be considered in the treatment of VHL patient. Orphan drug designation for Propranolol by EMA to treat von Hippel Lindau disease was achieved in 2017 (EU/3/17/1841).