Repurposing propranolol for the treatment of von Hippel-Lindau syndrome

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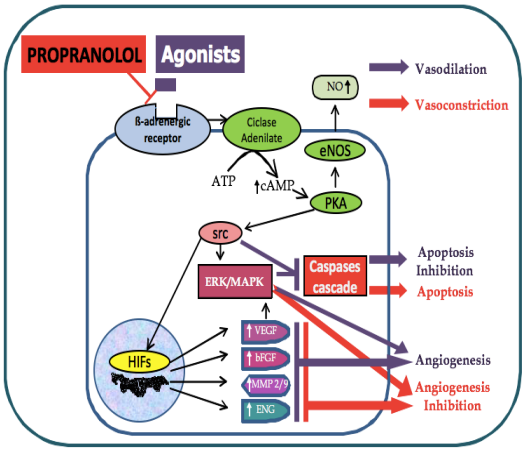
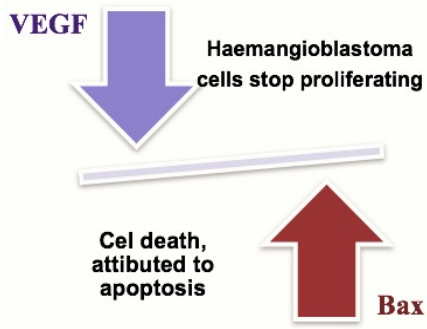
INTRODUCTION. ***Von Hippel-Lindau is a multisystem cancer syndrome*** that leads to the development of vascular tumors. Pathologically identical to the CNS hemangioblastomas, ***retinal hemangioblastomas***, are the most common and early sign, ***causing visual impairment:*** retinal detachment, retinal exudates, among others. Regular treatments include monitoring, laser photocoagulation, cryotherapy, antiVEGF administration, photodynamic therapy.

To date, no effective treatment in changing the course of the disease has been shown.

Propranolol is a-non selective β-blocker whose safety has been demonstrated. Because of its effectiveness, currently it is considered a first-line treatment for the infantile hemangioma, the most common vascular tumor in children. Recent studies have proved its possible use in other tumors (breast cancer, melanoma, cavernous hemangiomas), and it has also been attributed to it properties such as increasing the efficacy of chemotherapy. Albiñana *et al*. collected fresh tissue from surgically resected hemangioblastomas and developed primary cell cultures. *In vitro* assays were the hemangioblastomas were incubated for different times and concentrations, shown that ***propranolol decreases HIF expression levels*** and affects viability. Suggesting a ***potential role of propranolol as vasoconstrictor, antiangiogenic agent (inhibiting VEGF), and proapoptotic drug (leading to cell apoptosis).***



METHODS AND RESULTS. To evaluate the possible therapeutic effect of propranolol in VHL disease, a clinical trial including 7 VHL patients with juxtapapillary or peripheral hemangioblastomas was developed. All patients took 120 mg/day propranolol and were monitored at baseline and at 1, 3, 6, 9 and 12 months after. The primary endpoint of the study was the number and size of hemangioblastomas. On every visit alongside the treatment, retinas outcome as well as different biomarkers from blood samples were analyzed. As the main clinical outcomes, number and size of all the tumors present on the retina remained stable in all patients and no new tumors appeared. ***To highlight, the reabsorption of the exudation in the only two patients who had it initially, being progressive and clear.*** **These outcomes correlated with the decreasing of VEGF plasma levels from the first month of treatment in a significant manner (p<0.001), reaching normal levels (<50 pg/ml) in all cases after 3 months of treatment**. Moreover, a **decrease in the expression of tumor stemness genes (*Sox-2*, *Oct-4*), and proangiogenic genes (Epo and VEGF), and an increase in proapoptotic gene Bax was found**. As far as we know, these are the first biomarkers proposed to monitor the VHL disease activity.

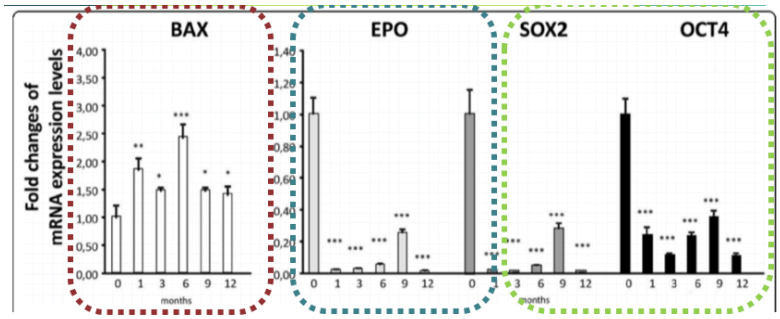


CONCLUSIONS. The results of this trial led to the **orphan drug designation** of propranolol by the European Medicines Agency EMA, to treat the VHL disease (EU/3/17/1841).

Propranolol may be used in the future for diseases where VEGF is involved, so new trials are needed. ***As peripheral blood levels of VEGF and miR210 correlated with retinal disease, they may be good biomarkers of the disease in the future.***

Albiñana, V., de las Heras, K. V. G., Serrano-Heras, G., Segura, T., Perona-Moratalla, A. B., Mota-Pérez, M., ... & Botella, L. M. (2015). Propranolol reduces viability and induces apoptosis in hemangioblastoma cells from von Hippel-Lindau patients. Orphanet journal of rare diseases, 10(1), 118.

Albiñana, Virginia, et al. "Repurposing propranolol as a drug for the treatment of retinal haemangioblastomas in von Hippel-Lindau disease." Orphanet journal of rare diseases 12.1 (2017): 122.



Increased Bax expression →APOPTOSIS

Decreased proangiogenic genes → EPO and VEGF

Decreased stemness genes → SOX and OCT4 → STOP TUMOUR PROGRESSION