

## **Anti-VEGF therapy mediated by lentiviral vectors for ocular diseases**

Yvan Arsenijevic<sup>1</sup>, Alexis-Pierre Bemelmans<sup>1</sup>, Marijana Samardzija<sup>2</sup>, Andreas Wenzel<sup>2</sup>, Christian Grimm<sup>2</sup>, Maite Cachafeiro<sup>1</sup>.

<sup>1</sup>Unit of Gene Therapy & Stem Cell Biology, Jules Gonin Eye Hospital, Lausanne, Switzerland; <sup>2</sup>Laboratory of cell biology, Zürich, Switzerland.

**Purpose:** The retinal balance between pro- and anti-angiogenic factors is critical for angiogenesis control, but is also involved in cell survival. We observed an upregulation of VEGF and photoreceptor (PR) cell death in the Light-damage (LD) model. Thus, we investigated the role of VEGF on the retina.

**Methods:** To characterize the action of VEGF during the LD, we exposed Balb/c mice subretinally injected with a lentiviral vector coding for a single chain antibody anti-VEGF (LV-anti-VEGF), or not, to 5'000 lux for 1h. We next evaluated the retinal function, PR survival and protein expression (VEGF, VEGFR1/2, Src, PEDF, p38MAPK, Akt, Peripherin, SWL-opsin) after LD. We analyzed Blood retinal barrier (BRB) integrity on flat-mounted RPE and cryosections stained with  $\beta$ -catenin, ZO-1, N-cadherin and albumin.

**Results:** In parallel to VEGF elevation during LD, extravascular albumin leakage and BRB breakdown were observed :  $\beta$ -catenin, ZO-1 and N-cadherin translocate to the cytoplasm of RPE cells showing loss of cell cohesion. Assessment of the retinal function reveals that PR rescue correlates with the level of LV-anti-VEGF expression and measures of the ONL thickness indicate that LV-anti-VEGF preserves by 82% the outer nuclear layer from degeneration. Outer segments (OS) appeared well organized with an appropriate length in the LV-anti-VEGF group compared to controls. Finally, LV-anti-VEGF treatment prevents BRB breakdown and maintained RPE cell integrity.

**Conclusions:** This study involves VEGF in LD and highlights the prime importance of the BRB integrity for PR survival. Taken together, these results show that anti-VEGF is neuroprotective in this model and maintains functional PR layer in LD-treated mice.

**Financial Disclosure:** No