Efficacy of umbilical cord derived mesenchymal stem cells (UC-MSC) in ischemic retinopathies.

Introduction:
Ischemic retinopathies, such as proliferative diabetic retinopathy (DR), and retinopathy of prematurity (ROP) are the main causes of severe visual impairment and blindness in adults and children, respectively. These disorders are generally characterized by an initial phase of retinal vascular obliteration (VO) followed by an aberrant intra-vitreal neovascularization (NV) which predisposes to retinal detachment and blindness [1]. Current ablative therapies (cryotherapy and laser photocoagulation) used clinically for the treatment of ischemic retinopathies are destructive. New treatment modalities such as anti-VEGF therapy, are promising but only tackle the pinnacle of the disorder, namely the NV; moreover, anti-VEGF is ineffective in ~25% of patients and may cause adverse effects [2]. Cell-based strategies for vascular repair are likely to arise from advances in regenerative medicine using stem cells. Bone marrow- and adipose tissue-derived mesenchymal stem cells (MSC) have been demonstrated to be effective as a therapeutic approach via their anti-inflammatory and tissue repair properties, as it was observed in various conditions such as cardiomyopathy, degenerative neuropathies, and ischemic-reperfusion injuries [3]. The umbilical cord (UC) serves as an abundant source of stem cells including presently relevant UC-MSC and endothelial progenitor cells. Moreover, UC-MSC differ from bone marrow and adipose tissue MSC, as they also express markers of pluripotent stem cell (Oct4, Nanog, and Sox2), and possess an inherent neurogenic and neurovascular potential [4], which would also be superior to the limited efficacy of endothelial progenitor cells from UC [5]. The efficacy of UC-MSC in ischemic retinopathies has never been investigated. Preliminary results from the host laboratory show that intravitreal (IVT) injected UC-MSC (tagged with red fluorescent protein [RFP]) were observed in inner and outer retina adjacent to vessels, and protected against retinovascular involution associated with the O2-induced retinopathy (OIR) model of ROP. Hence, UC-MSC seem to insert into newly formed vessels, and could participate in vascular network repair and development, through differentiation and possibly secretion of angiogenic and guidance cues.

Hypothesis:
Thus, we hypothesize that UC-MSC have a beneficial outcome in ischemic retinopathy by diminishing vascular depletion and promoting revascularization of the retina, through release of mediators and/or cellular differentiation.

Objectives and Methods (brief): Experiments will be conducted using the established mouse model of OIR [6].

1. Determine the efficacy of UC-MSC in salvaging the damaged retina by reducing VO and NV. For this propose, UC-MSC (+CD44,73,90,105,140b, and Oct4, Nanog, and Sox2; -CD34,45) will be isolated from umbilical cord of C57bl/6 mice at mid-gestation (embryonic age 8-15; [term: 19]). Preventive and reparative effects of UC-MSC will be evaluated by IVT injection of UC-MSC (or vehicle, or unrelated cell [eg. fibroblast]) at onset and at peak (3 days) of VO in OIR; OIR will be generated by placing newborn mice in 75% O2 for 5 days from postnatal day [P] 7 to 12. Retinas will be collected at different time points till P17 to determine the rate of revascularization and preretinal NV, by analyzing lectin-stained retinal vascular flat mounts. We anticipate UC-MSC to increase normal retinal revascularization and diminish intravitreal NV.

References: