NCX 1728, a nitric oxide (NO)-donating PDE-5 inhibitor, but not its des-nitro derivative (NCX 1880), enhances ocular perfusion and improves photoreceptor function in rabbits with endothelin-1 (ET-1)-induced ischemia/reperfusion injury of optic nerve head and retina

Dr. Corinna Galli

Senior Scientist
Nicox Research Institute, Milan, Italy

ARVO 2023; April 23 – 27 | New Orleans, LA, USA – Session # 331, Presentation # 2823

Background

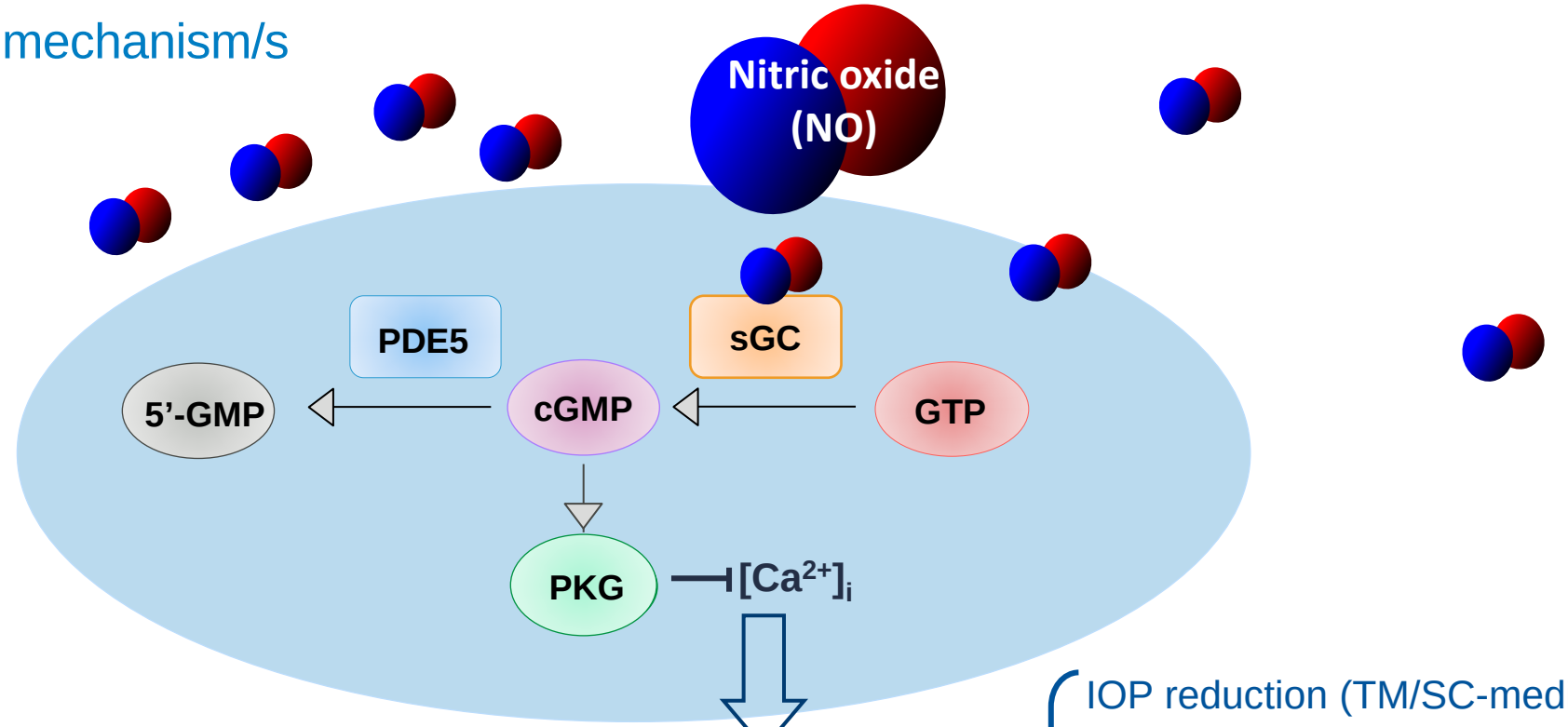
Nitric oxide (NO)/soluble guanylyl cyclase (sGC) signaling in the eye: relevance to retinopathies

- ✓ Ischemia/reperfusion contributes to optic nerve head and the retina degeneration in many ocular conditions[1]
- ✓ Nitric oxide (NO)/soluble guanylyl cyclase (sGC) plays a pivotal role in ocular blood flow and IOP homeostasis[2]
- ✓ Phosphodiesterase type-5 (PDE5) modulates the onset and duration of NO-mediated effects. PDE5 inhibitors have been proposed as ocular neuroprotective agents[3]
- ✓ NO-PDE5 inhibitors are a new class of compounds under development at Nicox for the treatment of retinopathies where dysfunctional ocular perfusion and neovascularization are key features in disease progression[4]
- ✓ NCX 1728 is an NO-donating PDE5 inhibitor currently in non-clinical development for back-of-eye diseases (for more info: https://www.nicox.com)

1. Wykoff et al., *Eye (Lond)* **2022**; 36: 249-256.
2. Cavet et al., *Invest Ophthalmol Vis Sci*. **2014**; 55: 5005-5015.
3. Holden & Wareham. *Neural Regen Res.* **2023**; 18: 1267-1268.
4. Pemp & Schmetterer. *Can J Ophthalmol*. **2008**; 43: 295-301.

Nitric oxide (NO)/soluble guanylyl cyclase (sGC) signaling pathway

Cellular/molecular mechanism/s



GTP: guanosine triphosphate
sGC: soluble Guanylate Cyclase
cGMP: cyclic guanosine monophosphate
PKG: cGMP-dependent protein kinase
PDE5: phosphodiesterase-5
5'-GMP: Guanosine 5'-monophosphate

Muscle cell relaxation

- IOP reduction (TM/SC-mediated)
- Vasodilation
- Enhancement of ocular blood flow
- Ocular tissues oxygenation

Sparing of ONH & retinal damage

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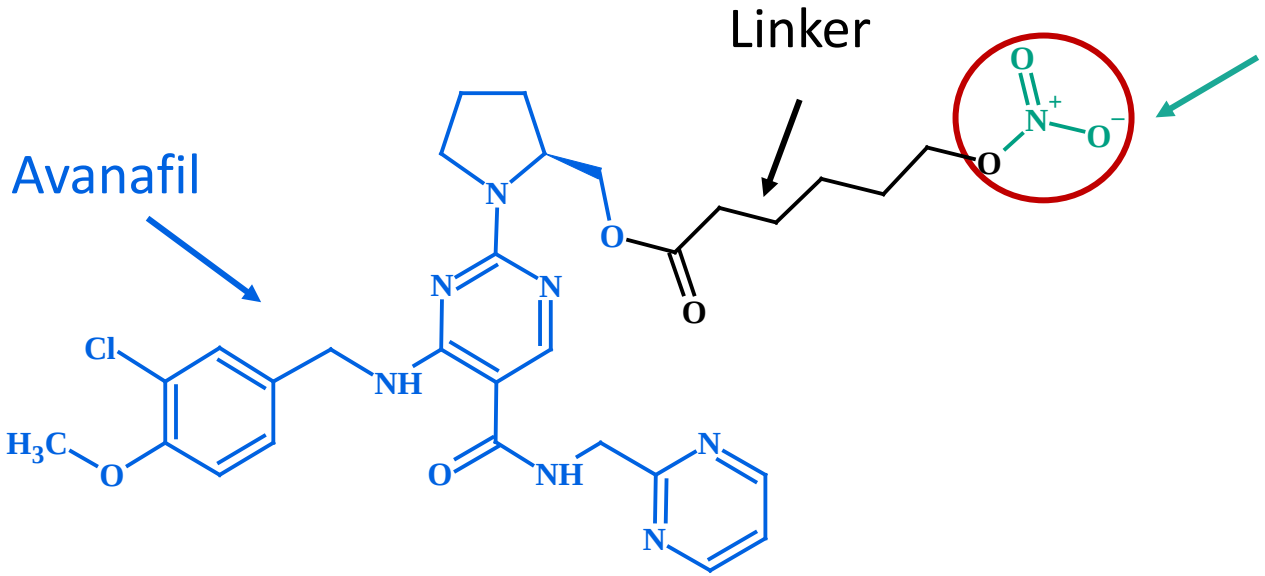
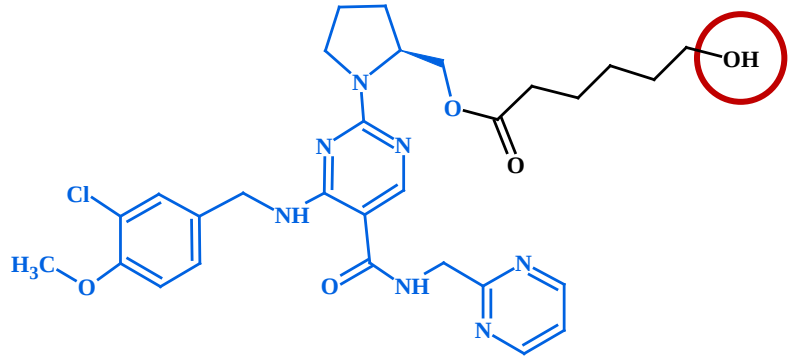
NCX 1728 (NO-donating avanafil) and NCX 1880 (des-nitro derivative of NCX 1728)

Chemical structure & physicochemical properties



NCX 1728
(NO-donating avanafil)
MW=643.09
cLogD (pH 6.7)=5.76



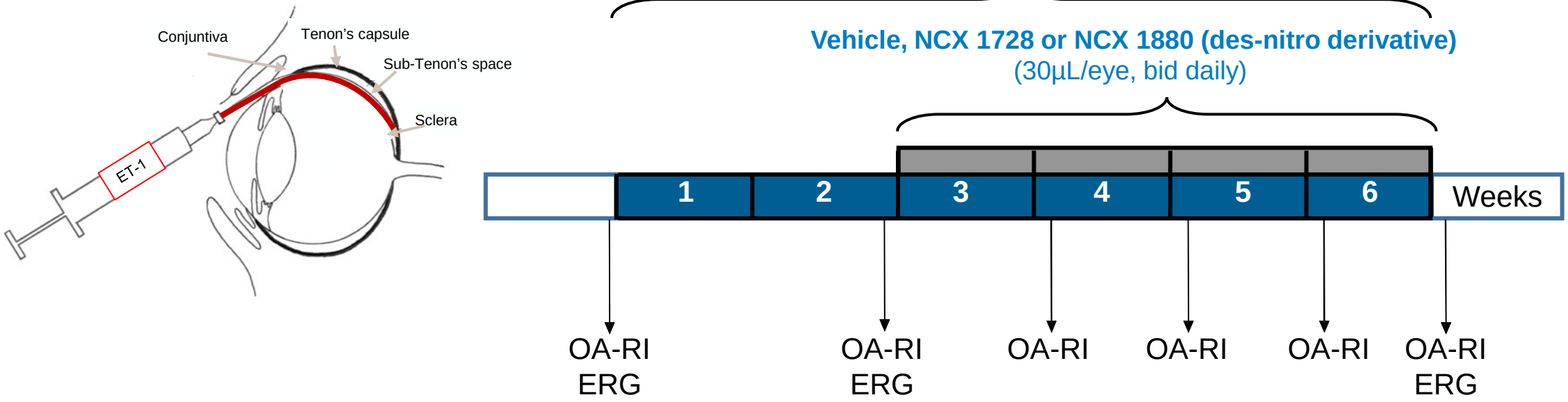
NCX 1880
(des-nitro derivative of NCX 1728)
MW=598.09
cLogD (pH 6.7)=4.47

Aim of the study

Explore NCX 1728-mediated effects on ocular hemodynamics and retinal cell physiology in a rabbit model of ischemia/reperfusion injury of the optic nerve head and retina

Endothelin-1 (ET-1)-induced ischemia/reperfusion injury of optic nerve head (ONH) & retina in New Zealand White rabbits[1]

Design & treatment schedule

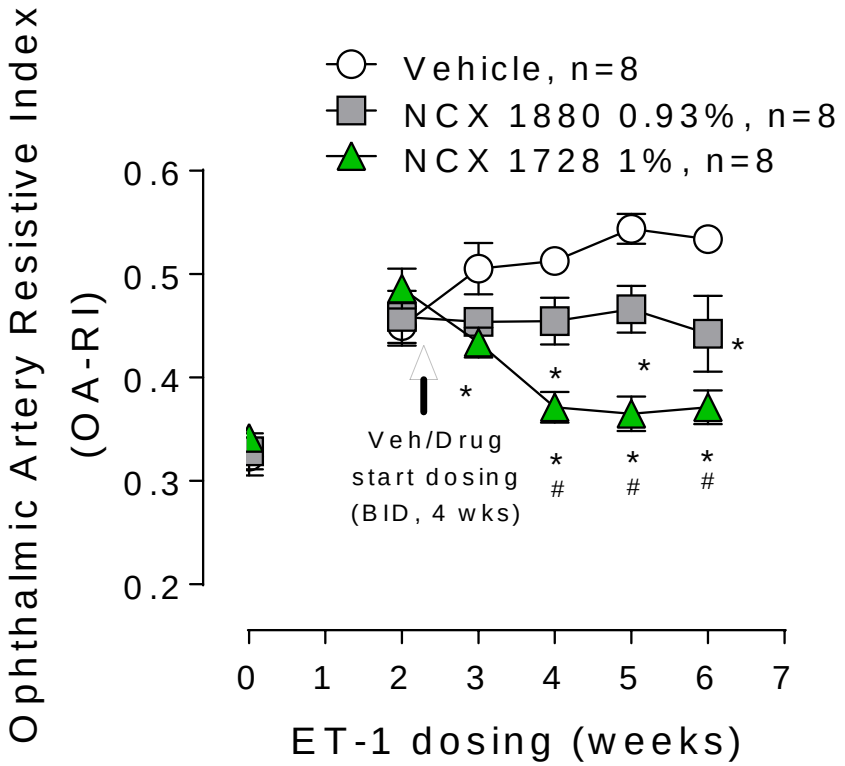


OA-RI, Ophthalmic artery resistive index; ERG, Electroretinogram
Vehicle: boric/phosphate buffer pH 6.7, Kolliphor EL, Myrj S40, Kollisolv PEG E 400, Ethylenediaminetetraacetic acid (EDTA) disodium salt and BAC

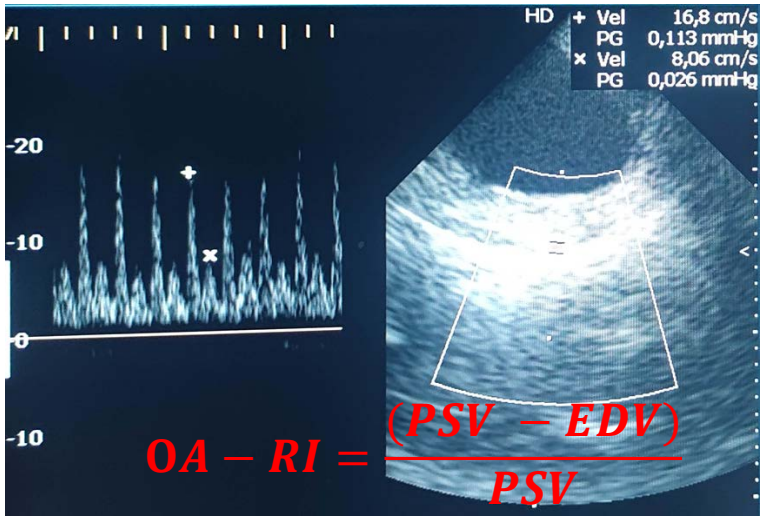
[1]Bastia et al., *J Ocul Pharmacol Ther*. **2022**; 38:496-504.

ET-1-induced *hemodynamic changes* following ischemia/reperfusion injury of optic nerve head (ONH) & retina in rabbits

NCX 1728 (NO-avanafil) vs. NCX 1880 (respective des-nitro derivative) – head-to-head study



REPRESENTATIVE ECOCOLOR DOPPLER IMAGE



PSV, Peak Systolic Velocity;
EDV, End Diastolic Velocity

**p<0.05 vs. vehicle; #p<0.05 vs. NCX 1880, Student's t-test.*

- NCX 1728 completely abolishes ET-1-induced hemodynamic changes
- NCX 1880 (des-nitro derivative) is only partially effective

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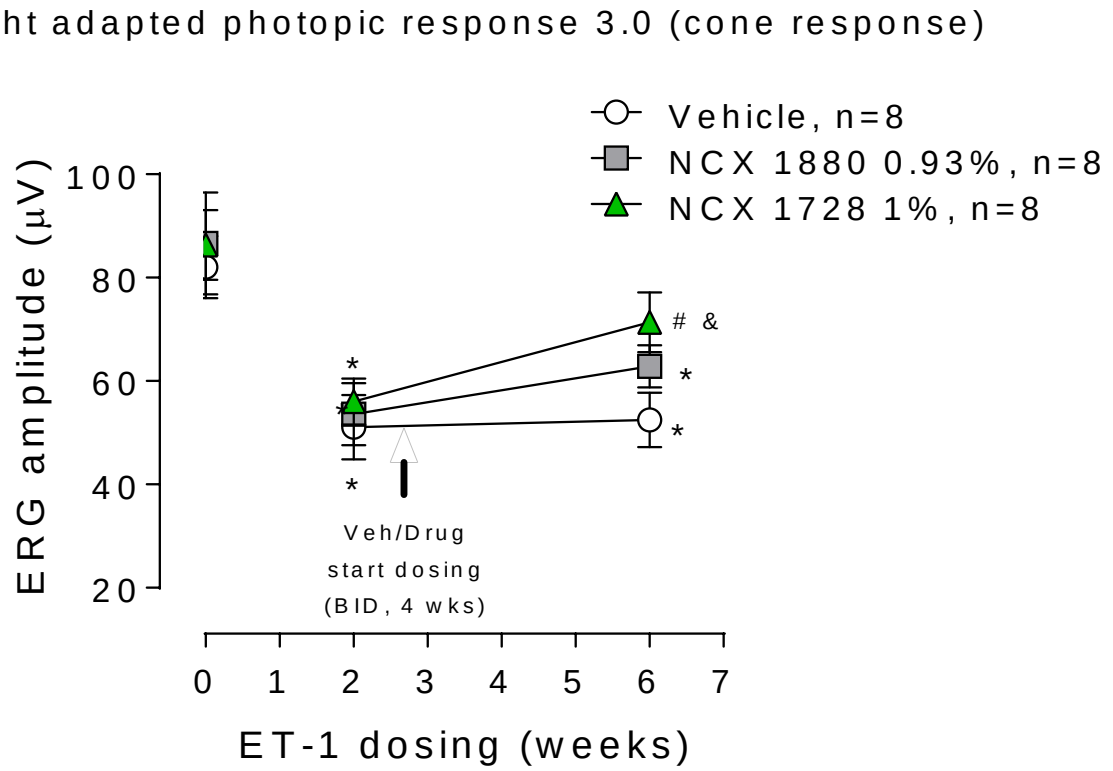
ET-1-induced *ERG changes* following ischemia/reperfusion injury of optic nerve head (ONH) & retina in rabbits

NCX 1728 (NO-avanafil) vs. NCX 1880 (respective des-nitro derivative) – head-to-head study



**p<0.05 vs. baseline; #p<0.05 vs. week 2; &p<0.05 vs vehicle, Student's t-test.*

- NCX 1728 abolishes ET-1-induced electroretinogram (ERG) changes
- NCX 1880 (des-nitro derivative) is partially effective

Concluding remarks

- ✓ NCX 1728 is a new molecular entity bearing two pharmacologically active moieties: NO and the PDE5-inhibitor Avanafil
- ✓ NCX 1728 reduces Ophthalmic Artery Resistive Index (OA-RI) following ET-1-induced ischemia/reperfusion injury
- ✓ NCX 1728 improves retinal cells activity and lowers IOP following ET-1-induced ischemia/reperfusion injury

NCX 1728 holds promise for the treatment of retinopathies where dysfunctional ocular perfusion and neovascularization are key features in disease progression

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Nicox Research Institute,
Bresso, Milan, Italy
&
Nicox Ophthalmics
Durham, NC, USA

https://www.nicox.com

- Emanuela Masini
- Laura Lucarini
- Silvia Sgambellone
- Silvia Marri

Dept. of Neuroscience, Psychology, Drug Research and Child Health (NEUROFARBA), Section of Pharmacology
University of Florence, Florence, Italy