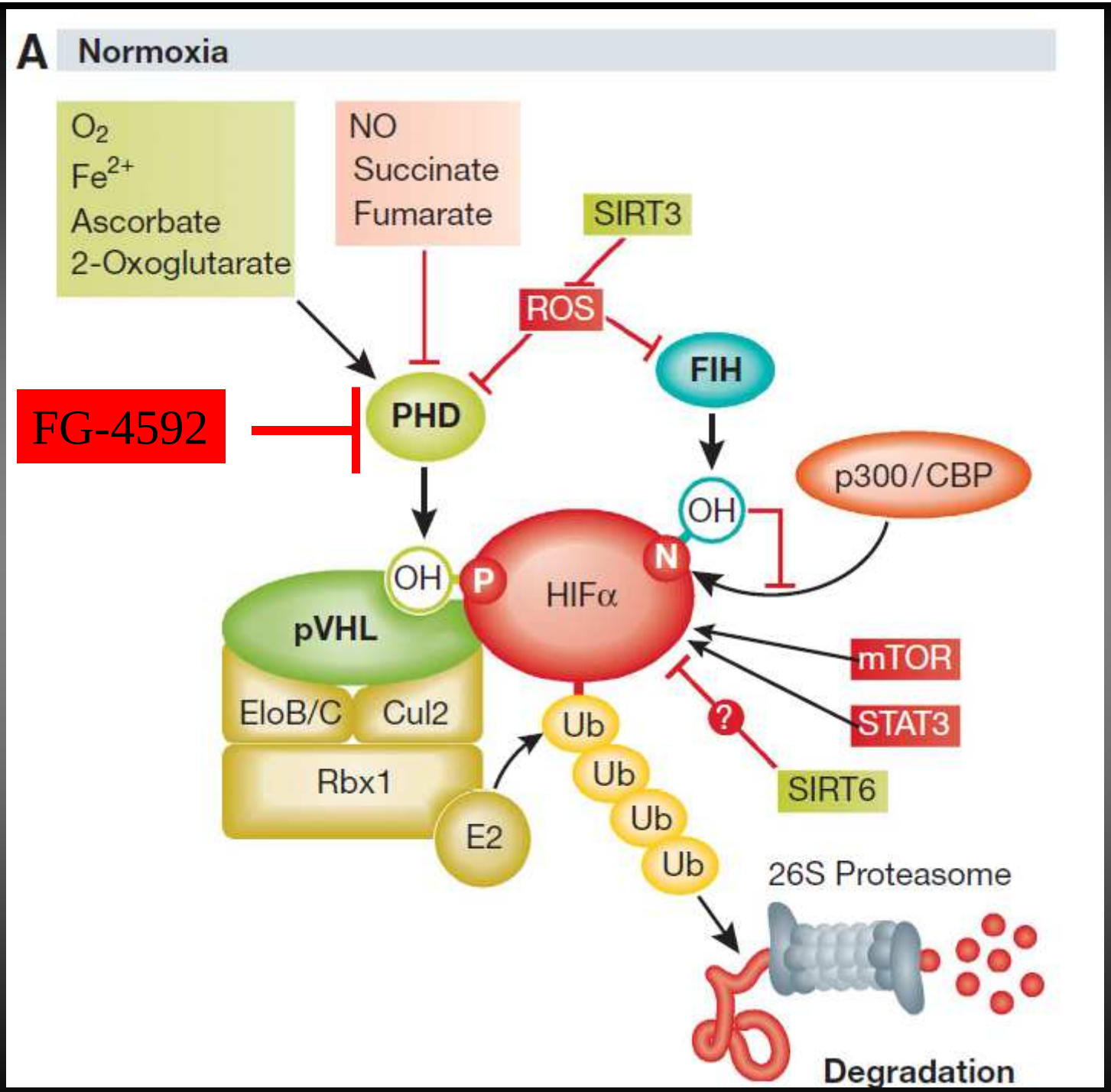
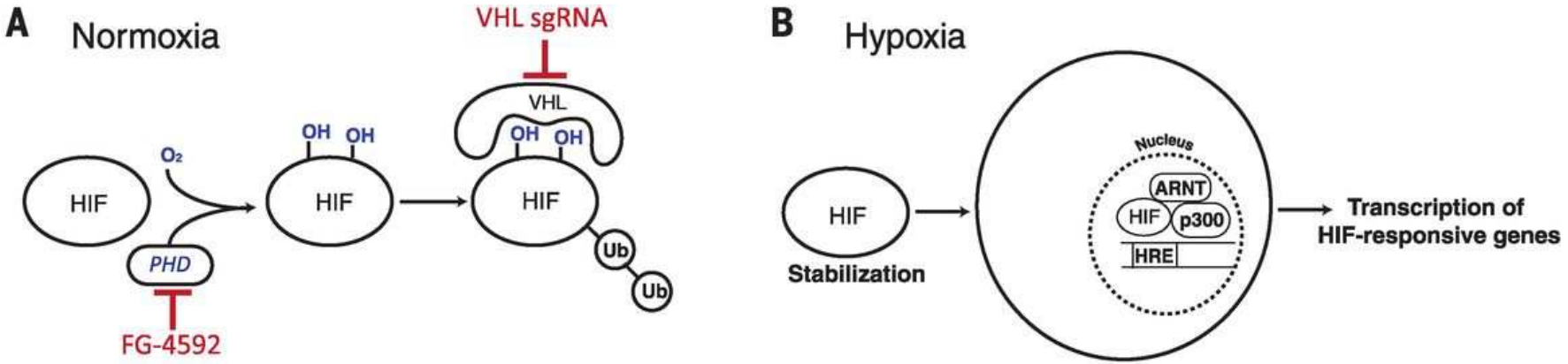
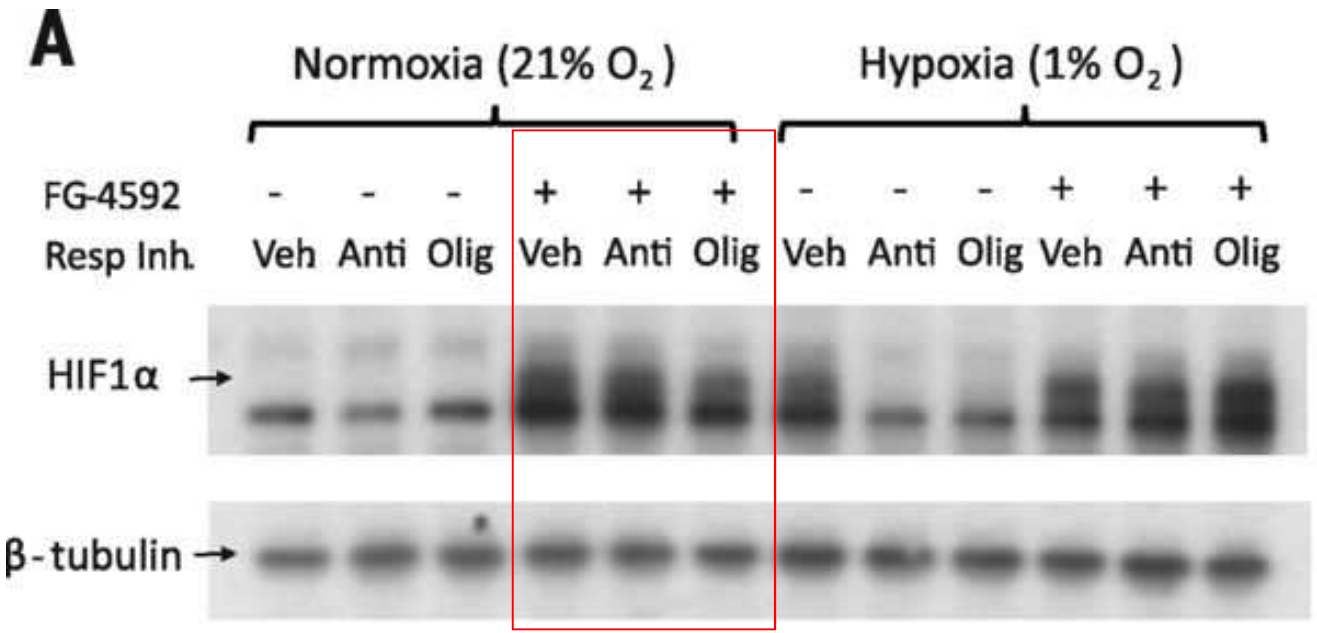

A Normoxia
O2
Fe2+
Ascorbate
2-Oxoglutarate
NO
Succinate
Fumarate
SIRT3
ROS
FIH
FG-4592
PHD
p300/CBP
OH
OH
P
N
HIFα
pVHL
EloB/C
Cul2
Rbx1
E2
Ub
Ub
Ub
Ub
mTOR
STAT3
?
SIRT6
26S Proteasome
Degradation

Fig. 2 Genetic or small-molecule activation of the HIF response is protective against multiple forms of RC inhibition, in multiple cell types.



act as competitive antagonists of 2-oxoglutarate, a cofactor that accepts one oxygen from molecular dioxygen to become succinate as the second oxygen forms trans-4-hydroxyproline

Fig. 3 FG-4592 causes normoxic stabilization of HIF1α and rewires energy metabolism.



HIF1α Immunoblot

± Respiratory chain RC inhibition with antimycin or oligomycin

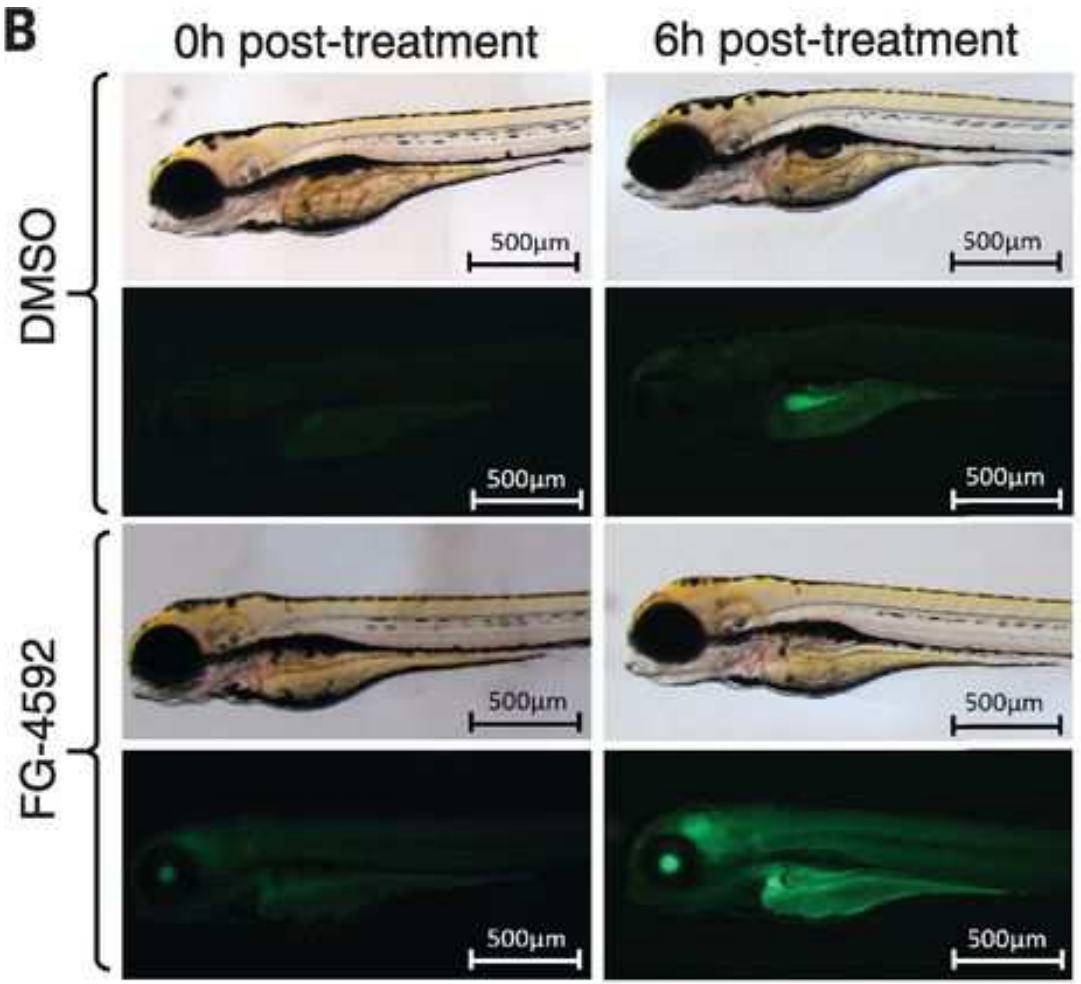
± FG-4592 under normoxia (21% O2) or hypoxia (1% O2)

RC inhibition prevents HIF1α stabilization during hypoxia

FG-4592 administration stabilizes HIF1α even during normoxia.

Isha H. Jain et al. Science 2016;352:54-61

FG-4592 treatment activates the HIF response in zebrafish embryos and alleviates death caused by Respiratoty Chain inhibition.



HIF-responsive promoter in Tg(phd3::EGFP)embryos

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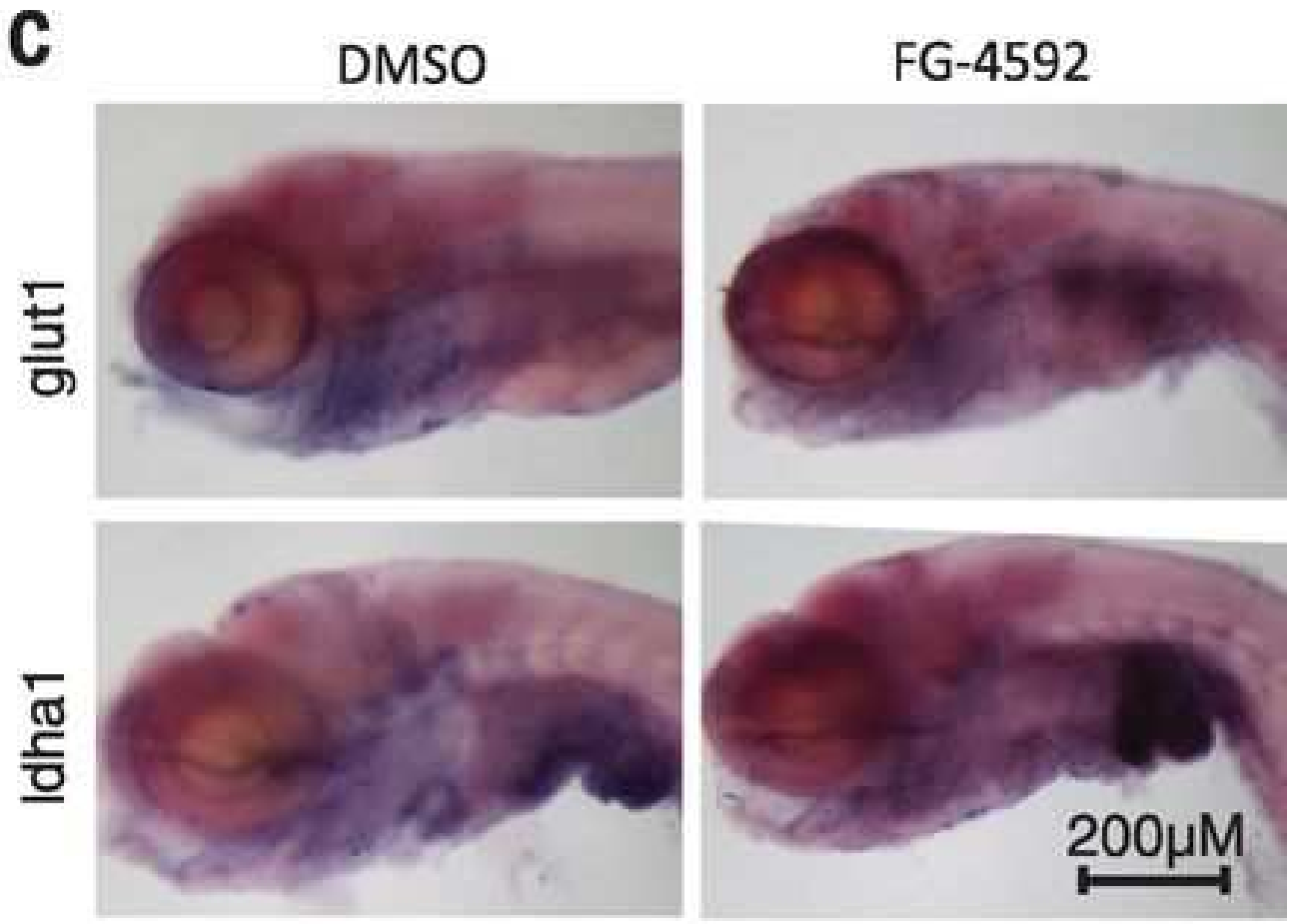
Isha H. Jain et al. Science 2016;352:54-61

FG-4592 treatment activates the HIF response in zebrafish embryos and alleviates death caused by Respiratoty Chain inhibition.



Known HIF targets glut1 and ldha1 are overexpressed in 96 hpf zebrafish embryos treated with FG-4592 for 6 hours

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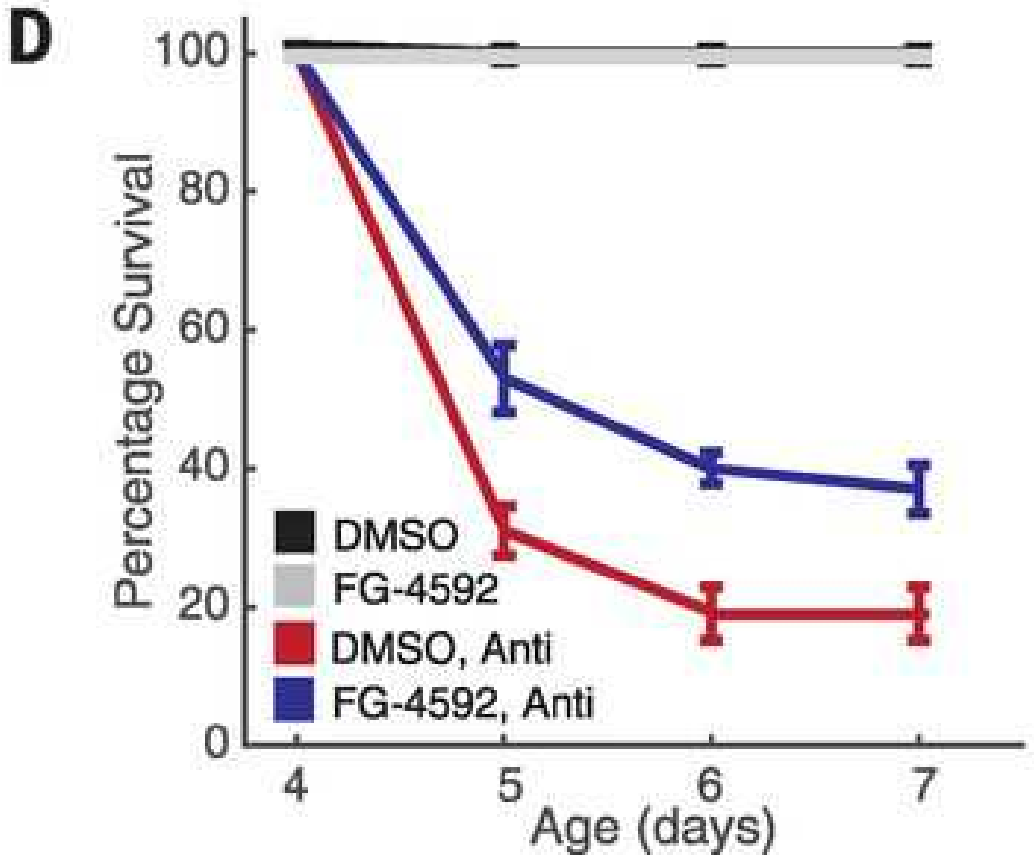
FG-4592 treatment activates the HIF response in zebrafish embryos and alleviates death caused by Respiratoty Chain inhibition.

Isha H. Jain et al. Science 2016;352:54-61



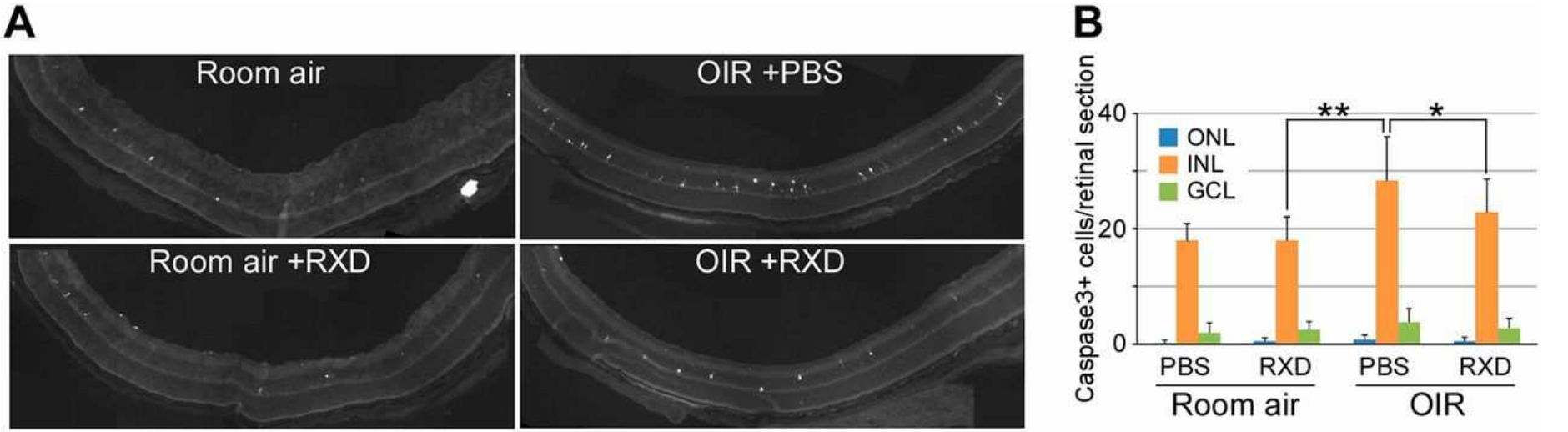
Exposure to FG-4592 rescues antimycin-induced zebrafish embryonic death.
RC inhibition by 2.5 nM antimycin in 4 days post fertilization (dpf) embryos results in significant death within the first 24 hours of treatment.
Coexposure of antimycin with FG-4592 (2.5 μM) doubles embryo survival, whereas FG-4592 alone has no impact.

Retinopathy of prematurity (ROP) causes 100,000 new cases of childhood blindness each year.
ROP is initiated by oxygen supplementation necessary to prevent neonatal death.

hypoxia-inducible factor (HIF) stabilization via HIF prolyl hydroxylase inhibition using the isoquinolone Roxadustat or the 2-oxoglutarate analog dimethyloxalylglycine (DMOG)
Roxadustat directs retinal HIF stabilization

Although both molecules conferred a protective phenotype
Roxadustat rescued the HIF-1 knockout mouse from retinal oxygen toxicity, whereas DMOG could not.
The simplicity of systemic treatment that targets both the liver and the eye provides a rationale for protecting the severely premature infant from oxygen toxicity.

Effect of Roxadustat on neural retina apoptosis.



FG-4592

Quantification of active caspase 3-positive cells demonstrates statistically significant reduction in apoptosis in the inner nuclear layer of animals treated with Roxadustat (RXD)

outer nuclear layer (ONL), inner nuclear layer (INL), and ganglion cell layer (GCL).

George Hoppe et al. PNAS 2016;113:E2516-E2525