PNAS: Welcome to Science Sessions. I’m your host, Chris Samoray. Retinopathy of prematurity, or ROP, is a common cause of childhood blindness. The disease occurs naturally in children born prematurely, and can be induced by the high oxygen supplementation levels used to prevent neonatal death. In a recent PNAS article, Jonathan Sears, a physician at the Cleveland Clinic Cole Eye Institute, and colleagues studied the potential of two drug treatments to prevent oxygen-induced retinopathy, or OIR, in mice. One of the drugs, Roxadustat, treated multiple ROP target areas, and might offer a systemic approach to combat oxygen-induced retinal injury in premature infants. The researchers were awarded the 2016 PNAS Cozzarelli Prize in Biomedical Sciences for their work. I spoke with Sears about the work at the Academy’s annual meeting, and he described what makes the retina of premature infants susceptible to ROP.

Sears: The primary principle here is that oxygen resuscitation for these children is paradoxical. Oxygen is necessary to keep these children alive, but at the same time it’s toxic to premature developing tissues that are very susceptible to the abnormally high level of oxygen. The typical saturation for the fetus is between 85-92% in utero. When these children are born, in order to sustain their life, it is often necessary to keep those oxygen tensions and saturations at a very high level, sometimes greater than 95%.

PNAS: The high oxygen levels cause severe damage to vascular growth and blood vessels in the retina. The processes that lead to this destruction involve the degradation of the alpha subunit of hypoxia-inducible factor, or HIF, a protein induced by low levels of oxygen that directs many facets of cell survival and development. In the PNAS article, Sears’ team studied the potential of two small-molecule HIF stabilizers, DMOG and Roxadustat, to prevent OIR in mice. Sears explains why these two drugs were studied in particular.

Sears: It’s very important to remember that the eyes reflect systemic disease. Retinopathy of prematurity is a reflection of oxygen toxicity in all of the organs of the developing child. Therefore, our plan was to use the phenotype of the eyes, or the condition of the eyes, to tell us how the rest of the body was doing.

Our plan in this experiment was to compare the cellular response of an agent that targeted only the liver to a medicine that targeted both the liver and the eye. We used a process called systems pharmacology to look at the transcriptional profile of both the liver and the retina to compare their responses to both these drugs.

The reason we chose these two drugs was that Roxadustat has a very similar structure to DMOG, but Roxadustat actually circumvents the liver to also target the retina. We used these two drugs because we know quite clearly in prior studies where we knocked HIF-1-alpha out of the liver that if you tried to rescue these retinas with DMOG, it was unsuccessful because the target of the systemic medication was the liver. Therefore, we felt it was very important to use a systemic medication that would facilitate protection of the retina.
**PNAS:** The analyses indicated that both DMOG and Roxadustat conferred a level of protection against OIR in the mice. But unlike DMOG, Roxadustat targeted liver and retina HIF pathways. Additionally, both molecules helped prevent oxygen-induced injury to other organs, such as the lung. Sears says the findings are significant for a couple of reasons.

**Sears:** Number one the demonstration that simultaneous treatment of ocular disease also prevented lung disease means that this is a strategy that would be very happily incorporated by neonatologists because we could help them create a process by which the neonate could exchange gas. And this in turn, would feed forward to protect the eyes because we would need less oxygen to keep those children alive. Most importantly, it showed that if you used a compound such as Roxadustat, you would have to use it at a very low dose. And the reason is that it targets this giant warehouse, which is the liver, and it also targets the eye. So, it has this synergy or additive strategy that confers protection to distill capillary beds by targeting both the liver and the eye simultaneously.

**PNAS:** I asked Sears how he felt about being awarded the Cozzarelli Prize in Biomedical Sciences for the study.

**Sears:** I have to admit I’m humbled. I must tell you that it’s my coauthors that really deserve this. I feel very proud that our work is recognized in this way. I’m hoping that this will be an impetus or a jumpstart so that it can be translated for children. I think this recognition by the National Academy of Sciences suggests that there is broad appeal to this strategy in the scientific community, which is most important to making sure therapy can become a reality.

**PNAS:** Podcast interviews with all the 2016 Cozzarelli Prize winners can be found at pnas.org/multimedia. Thanks for listening to Science Sessions.