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OPTIC NERVE HYPOPLASIA IN CHILDREN

CANCER CELLS vs STEM CELLS

HELPING PATIENTS MAINTAIN CORNEAL STEM CELLS

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EYE ON THE FUTURE

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Optic Nerve Hypoplasia in Children

"A Disease of Brain Development"

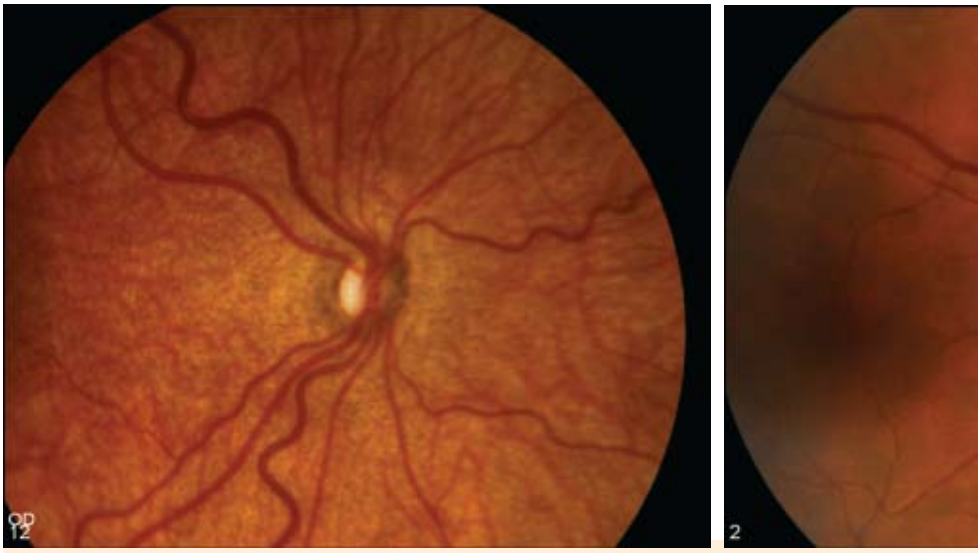
by Allyson T. Collins

Prior to 1970, fewer than 30 cases of optic nerve hypoplasia (ONH) had been reported in English publications throughout the world. But this congenital condition, defined by small optic discs in one or both eyes, seems to have become more prevalent in the past decades. Few North American studies have quantified the prevalence of ONH, but a 1997 study in Sweden found it to be the most common eye disease causing blindness in children.

Dr. Mark Borchert, head of The Vision Center at Childrens Hospital Los Angeles and associate professor of ophthalmology and neurology at the Keck School of Medicine of the University of Southern California, says that his experience with patients at CHLA supports this trend.

"Optic nerve hypoplasia seems to be an epidemic at the present time," he says. "I now see about three new cases a month of this condition."

About 80 percent of children who have ONH are affected in both eyes, and visual acuity can range from no light perception to near-normal vision. Dr. Borchert says that doctors are unsure of the condition's cause, though it does not appear to be hereditary.



L-R: Optic Nerve with Hypoplasia and Normal

A Complex Condition

Because ONH presents in children who have poor vision, it could be interpreted as solely an eye disease; but Dr. Borchert calls it a disease of brain development.

"The optic nerve is part of the brain," Dr. Borchert explains. "These children with ONH have miswiring and lose neurons in many parts of their brain, resulting in other developmental problems. The vast majority turn out to have serious learning disabilities, motor problems and issues with speech and communication."

Dr. Borchert says that these additional problems are due to the disease's impact on the hypothalamus, which helps regulate the pituitary gland.

"It turns out that 70 to 80 percent of these children have pituitary hormone problems," he says.

In their research, Dr. Borchert and his colleagues have determined that thyroid hormone deficiency is second only to growth hormone deficiency in these patients, and that 98 percent of children who have both ONH and hypothyroidism are severely retarded.

Doctors have known for decades that thyroid hormone deficiency is responsible for the condition cretinism, and have been screening infants for this deficiency since the 1970s. While many states consider high levels of thyroid stimulating hormone (TSH) a marker for hypothyroidism in infants, high TSH levels in children with ONH and hypothyroidism can be due to a malfunctioning hypothalamus.

Dr. Borchert believes that a simple tweak of the testing policy – reporting both high and low levels of TSH – could make a significant difference.

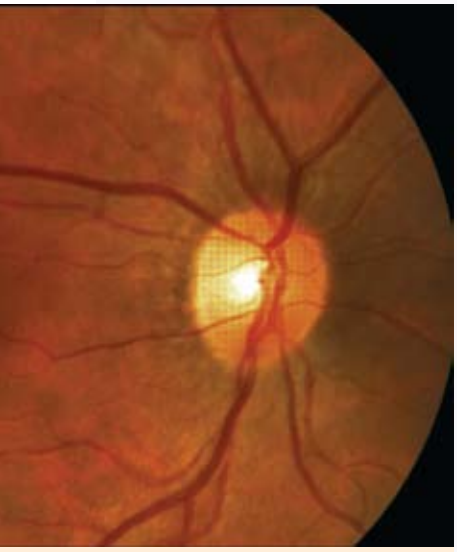
"If we just change the way we report the test without changing the test at all, we could identify these kids at birth, and theoretically prevent mental retardation," he says. "And not only would we detect the hypothyroidism, at the same time we may

actually be able to make a diagnosis of ONH."

Changing Public Policy

To prove a possible need for changes in infant screening policies for hypothyroidism, Dr. Borchert and his colleagues are looking to their national database of thousands of children born with ONH. When a family registers for the online database, they provide information including where the mother lived before and during the first six months of pregnancy, as well as after the child's birth.

"Every state in the union screens for thyroid disorders," Dr. Borchert explains. "Some measure thyroid hormone directly, others measure thyroid-stimulating hormone, and some measure both."



Optic Nerve

Researchers at The Vision Center plan to use this information to determine which laboratory testing and reporting methods are most effective for early detection of the condition.

"Then we can recommend the best and most cost-effective method for detecting ONH and hypothyroidism in every child," Dr. Borchert says.

"With that information, we may be able to impact public policy and establish a unified national testing standard."

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Mark S. Borchert, MD, is director of the Eye Birth Defects and Eye Technology Institutes in The Vision Center at Childrens Hospital Los Angeles, and head of CHLA's Division of Ophthalmology.
Dr. Borchert is also an associate professor of ophthalmology and neurology at the Keck School of Medicine of USC and the Doheny Eye Institute.

The Vision Center at Childrens Hospital Los Angeles (CHLA) serves as the pediatric ophthalmology arm of both the Doheny Eye Institute and the Keck School of Medicine of USC. It includes six institutes: the Retina Institute, the Cornea Institute, the Eye Birth Defects Institute, the Vision Development Institute, the Eye Technology Institute and the Orbit and Eye Movement Institute.

"This is the largest pediatric ophthalmology division in the country," says Dr. Mark Borchert, head of The Vision Center. "We see more patients and have more full-time faculty than any other program." This includes more than 12,000 pediatric patients treated each year.

In addition, The Vision Center is one of just six departments at CHLA to receive the distinguished qualification of "Center of Excellence" for its clinical and research accomplishments.

This distinction has helped boost fundraising support for The Vision Center, especially in the form of contributions from the family of the founding benefactors, Alyce and Michael Dalany. While The Vision Center receives funding from outside foundations and the National Institutes of Health for research projects, laboratory testing and patient-related costs, the Dalany's donations support research staff, including biostatisticians and clinical research coordinators, who are involved in multiple projects.

"The Dalany funds allow us to have the flexibility to take on pilot studies that we could not undertake without having certain critical research personnel," Dr. Borchert says. "Since we have a wealth of patients here with very unusual eye diseases that are often understudied, we can mine this wealth of patient research if we have key personnel that are funded unconditionally, no matter what they are studying."

Another influential figure to take note of The Vision Center's accomplishments has been Dr. Henri Ford, vice president and chief of surgery at CHLA.

"Dr. Ford has been one of The Vision Center's biggest proponents within the hospital and the university," Dr. Borchert says. "He has been a wonderful leader for us and has also agreed to serve as chairman of our advisory board, in spite of the fact that he has so many other important jobs. His leadership has been unparalleled."

Translating Research to the Clinical Setting

Cancer Cells vs Stem Cells

By Allyson T. Collins

Humans generally have two major fears, says Dr. Thomas Lee, director of the Retina Institute at The Vision Center at Childrens Hospital Los Angeles. The first, Dr. Lee says, is the fear of death from cancer. The second is fear of going blind.

These two concerns can become a reality with one eye disease – retinoblastoma, an aggressive, malignant tumor in the retina that affects about 250 American children each year, according to the National Institutes of Health.

But recognizing a twist of nature, Dr. Lee, along with Dr. Linn Murphree and colleagues at The Vision Center and the Doheny Eye Institute, believe that the same genetic pathways involved in initiating growth of a retinoblastoma may also prove beneficial in creating new treatments for eye diseases.

"Our work is designed to delve into both fields," Dr. Lee says. "Our hope is that by understanding how retinal cells divide, we can harness that information to stop the process in the setting of cancer and start it when we want to make new cells to replace damaged or diseased ones."

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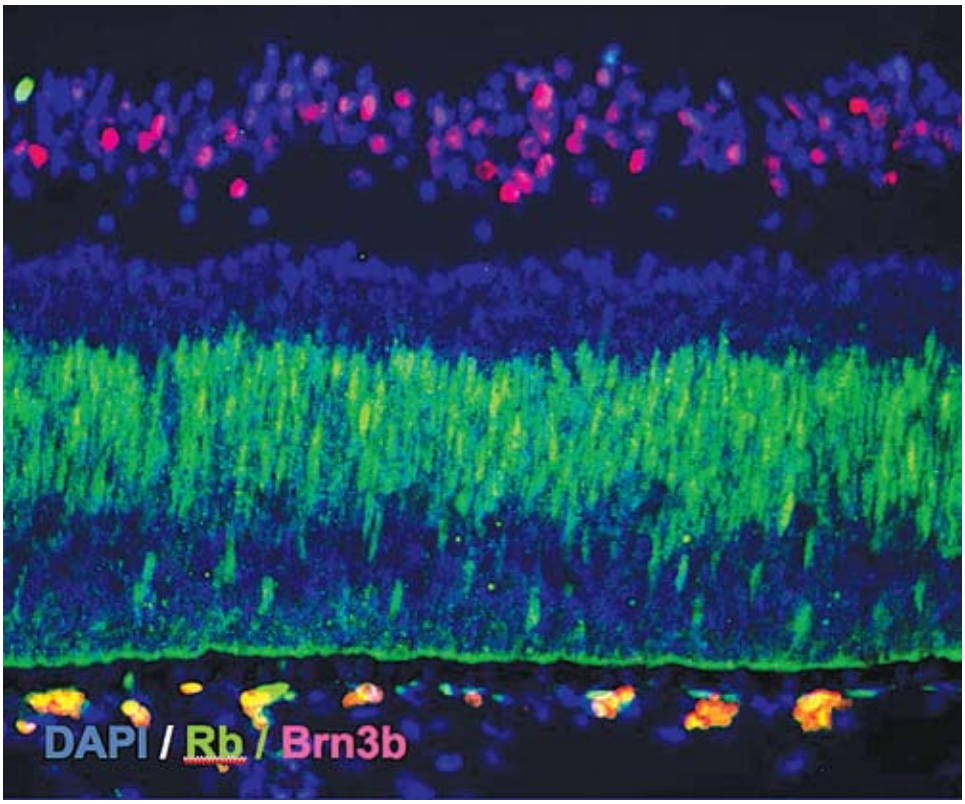
At The Vision Center, children from around the world stand to benefit from this research of retinal stem cells; young patients from the U.S., Canada, Jordan, China and Bulgaria, among other countries, receive retinoblastoma treatment at Childrens Hospital Los Angeles.



The Developing Human Retina
The green cells are proliferating retinal progenitor cells that are expressing the retinoblastoma protein (pRb). The purple cells are immature ganglion cells that have just been created and express a marker Brn3B.

Harnessing the Potential

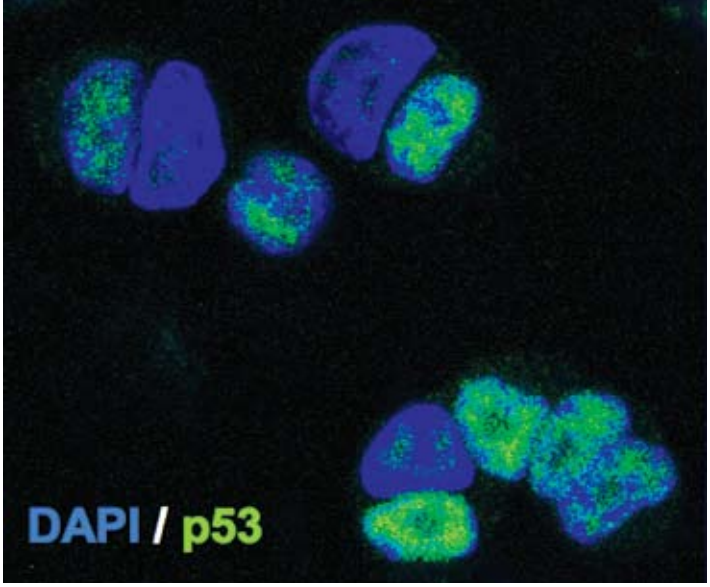
"Our interest in retinal stem cells in part evolved out of all the excitement surrounding stem cells in general," says Dr. Lee, who has been practicing at The Vision Center for the past two years.

Dr. Lee estimates that the topic of stem cells only entered the mainstream press in about the year 2000. Embryonic stem cells were actually identified in the early 1960s by Canadian researchers Ernest A. McCulloch and James E. Till.

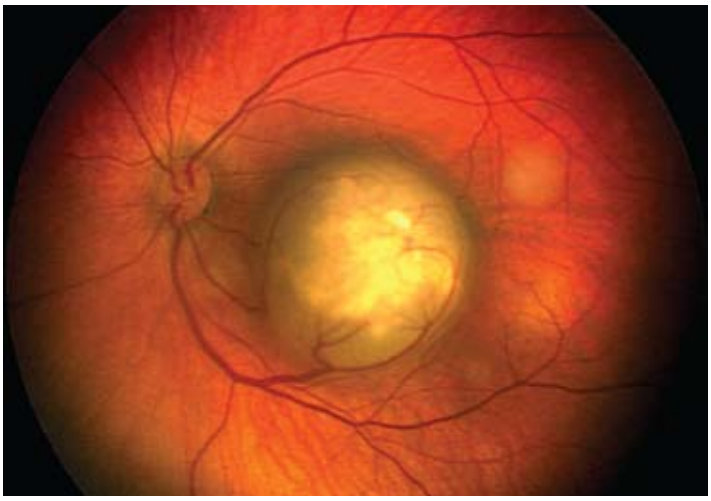
Still, Dr. Lee says, "There has been a big hurdle in trying to harness the potential of these cells, and in understanding how these cells are regulated and how we can control them. How do we go from a single fertilized cell to more than one hundred trillion cells?"

He likens the work of stem cells in the body to a biological human resources department, in which cells must be identified, recruited and positioned in the right tissue at the right time to perform a specific function.

Even more than four decades after the discovery of stem cells, Dr. Lee says, "we're still only scratching the surface" of understanding how they work.



Retinoblastoma cells that have been induced to express the p53 protein (green). The blue is a non-specific nuclear DNA stain. This protein is critical in determining whether proliferating cells can continue to divide or whether they will stop/die.



Fundus photo of a two-week-old child with a history of bilateral retinoblastoma. There are several tumors present (one large, one medium, and three smaller ones barely visible).

Cancer Cells Versus Stem Cells

From the time of McCulloch and Till's discovery until recently, many research scientists had maintained that cancer cells and stem cells belonged in distinct domains.

"In the past 10 years, those two areas have come closer and closer together, and now we recognize that they actually overlap to an extent," Dr. Lee says. "Now we realize that the cells that drive cancer are very similar to stem cells. There are actually malignant stem cells within a tumor."

Some researchers, including Dr. Lee, believe that cancers such as retinoblastoma may arise from organ-specific stem cells. Therefore, looking at the genetic pathways of stem cells may provide insights into their cancerous changes.

Dr. Lee's team is working on identifying genes that drive the proliferation of all retinal cells – malignant and therapeutic. "By studying this area you actually get a bigger bang for your buck," he says.

The first question that must be answered before pursuing this research, however, is whether retinal stem cells exist. Scientists have known that other species, such as zebrafish and salamanders, are able to regenerate their retinal tissue. In the past 10 years, researchers have also found cells that could be taken from the anterior part of the mammalian retina known as the ciliary marginal zone, and induced to divide and form retinal cells in culture.

But the larger question is whether these cells can function in a therapeutic way. "This has been the biggest sticking point," Dr. Lee says. "It's one thing to get cells to grow in culture, but it's a whole different thing to get them to function like a photoreceptor."

Understanding Stem Cells

In light of this challenge, Dr. Lee's current work involves three primary goals: determining the precise role of stem cells in ocular tumor formation; identifying genes that enhance stem cell growth from within stem cells; and looking beyond stem cells to external factors that can impact and nurture their development.

"An infant needs a whole group of people around it to help it survive," Dr. Lee says. "If it doesn't have a family, it won't grow."

Dr. Lee likens this scenario to the microenvironment necessary to foster retinal stem cell development. "We're trying to understand how the environment can manipulate cell growth and function," he explains. Dr. Lee and his colleagues would like to translate this work from the laboratory to the clinical setting for the benefit of patients at Childrens Hospital Los Angeles and children everywhere.

"By studying this process that comes at the intersection of cancer and blindness, we can hopefully make a difference for children who have retinoblastoma," he says.

Thomas Lee, MD, is the director of the Retina Institute at Childrens Hospital Los Angeles. Dr. Lee is professor of ophthalmology at the Keck School of Medicine of USC and the Doheny Eye Institute. He specializes in retinopathy of prematurity and retinoblastoma, along with other challenging retinal diseases.