UCLA Jules Stein Eye Institute

CLINICAL UPDATE

Discoveries Pave the Way Toward Improved Treatment of Ocular Melanoma

Several recent advances reported by the Stein Eye Institute Ophthalmic Oncology Center (OOC) could change how physicians manage patients with ocular melanoma and point the way toward better treatments and a potential cure for the most common eye cancer in adults.

Ocular melanoma, which forms in the pigmented layers of the choroid under the retina, is diagnosed in approximately 2,000 new patients each year. When the eye is treated, the growth of the tumor can be controlled. Standard radiation treatment of the melanoma, however, usually results in radiation damage and vision loss. Moreover, no matter how well the tumor is treated in the eye, there is a significant risk of the cancer spreading outside the eye to the liver or other parts of the body.

Three recent papers by a team at Stein Eye Institute headed by Tara McCannel, MD, PhD, assistant professor of ophthalmology and director of the OOC—the largest center treating ocular melanoma on the West Coast—have major implications for changing the field.

Ultrasound Improves Surgical Results

In one study, published in the May 2012 issue of the journal *Ophthalmology* and featured in the American Academy of Ophthalmology's newsletter, *Academy Express International*, Dr. McCannel and colleagues found that the use

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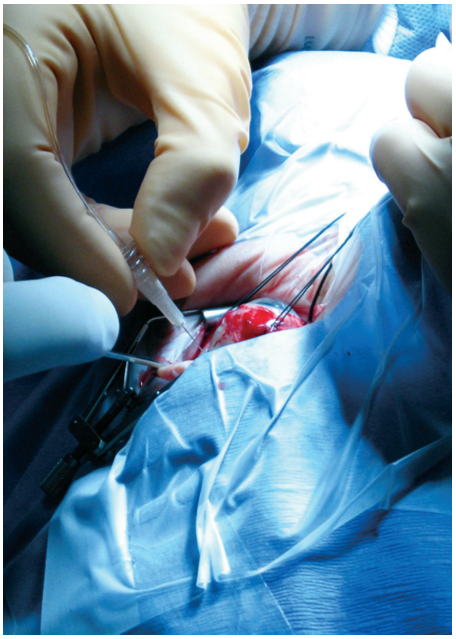

Fine needle biopsy during ocular melanoma treatment surgery.

Successful Gene Therapy Method for LCA Could Also Deliver Gene for Usher 1B

A Stein Eye Institute research team has found that a vector successfully employed as a delivery vehicle in the well-publicized gene therapy trial for Leber congenital amaurosis (LCA) can also be used to deliver *MYO7A*, the gene for Usher 1B syndrome, to retinal cells. The discovery could lead to clinical trials of this gene therapy strategy for Usher 1B patients, who are born deaf or with profound hearing impairment, and who gradually lose their vision to retinitis pigmentosa. Usher syndrome is the most common form of combined deaf-blindness, affecting one in 23,000 people in the United States.

"Our findings suggest the possibility that blindness in Usher 1B can be prevented by using this well-tested gene therapy

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of ultrasonography improves the results of plaque surgery outcomes for ocular melanoma patients. By using ultrasound for patients at the time of the initial surgery, her group was able to improve the accuracy of the plaque positioning and eliminate local recurrence for the surgical cases at OOC—results significantly better than those reported in the Collaborative Ocular Melanoma Study, as well as at other centers that treat this cancer.

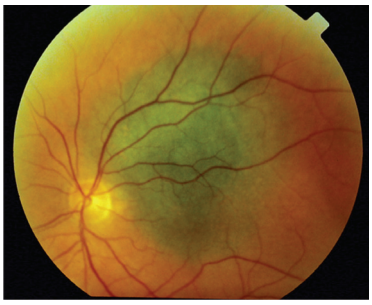
"The current literature regarding standard radiation treatment for ocular melanoma suggests that a 10 percent failure rate is acceptable," notes Dr. McCannel. She adds that the prevailing thinking among colleagues across the country has been that the surgery's success rate was good enough to continue without the use of imaging, which takes additional time and personnel, as well as requiring an ultrasound machine to be in the operating room. "People are used to doing things a certain way, and there can be resistance to adding another step to the procedure," Dr. McCannel says. Her group reported, however, that ultrasonography during surgery results in repositioning the plaque to a more accurate position in one out of three cases. "Even though we use all sorts of clinical parameters that are very useful, employing the ultrasound for the final measurement provides increased accuracy," Dr. McCannel confirms.

> Dr. McCannel's group reported that ultrasonography during surgery results in repositioning the plaque to a more accurate position in one out of three cases.

Virtually eliminating failure for the primary treatment significantly reduces patient morbidity, and as Dr. McCannel notes, it means patients do not require a repeat treatment and the additional radiation that goes with it. Moreover, when the first treatment fails, it commonly leads to the need to remove the eye. "If you radiate the eye twice, there may be increased ocular damage from receiving additional radiation," Dr. McCannel explains. "If the tumor returns, it indicates that the tumor is not being controlled, so the eye is usually enucleated in that circumstance."

Fine-Needle Biopsy Proven Safe

Recent molecular discoveries now allow the risk for cancer spreading to the liver and other organs to be determined by a needle biopsy. Just as tradition has played a role in the resistance of many centers to use ultrasonography at the time of the initial ocular melanoma surgery, long-held beliefs about potential risks have prevented most ophthalmologists from using fine-needle aspiration biopsy to gain prognostic information on ocular melanoma patients. "The concern has always been that if you touched the tumor you might cause the cancer to spread throughout the body, so you manipulated the eye as little as possible and just carefully applied the radiation to treat it," Dr. McCannel says. "That's the way it's been done for decades." Since first pioneering biopsy in patients with ocular melanoma for metastatic prognostication at Stein Eye Institute, Dr. McCannel's group has encountered skepticism from centers that remained uncertain about its long-term safety for patients.



Ocular melanoma involving the macula of the left eye.

But in the longest follow-up on the safety of needle biopsy for ocular melanoma patients, published in the March 2012 issue of *Ophthalmology*, Dr. McCannel and colleagues showed that with up to six years of follow-up the biopsy resulted in no local complications and that biopsy does not increase the risk of spreading the cancer elsewhere in the body. Other groups have reported similar findings. "We now know that if the cancer metastasizes, it is because the tumor's molecular makeup is such that it is going to spread independent of the physical manipulation of the tumor through the biopsy," Dr. McCannel says.

The findings suggest that centers should consider needle biopsy to obtain prognostic information that can better inform patients about the level of aggression of their tumor. "Until now we've had no way of knowing how these patients would do," Dr. McCannel says. "We would treat the eye and monitor it for the rest of the patient's life, looking at the liver and hoping the disease didn't come back. Now we can give patients much more information. Clinical trials are also emerging for patients with high metastatic risk, whose cancer has

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not yet spread. Patients must be made aware of all their options." Several years ago, Dr. McCannel's group collaborated with a team of UCLA health psychologists on a study in which they interviewed patients and found that the overwhelming majority wanted the prognostic information, even if there was no cure for their disease.

Beyond the prognostic information, the biopsy results have the potential to affect the way ocular melanoma patients are managed. Dr. McCannel notes that higher-risk patients are receiving more intensive screening protocols to determine if their cancer might spread to the liver.

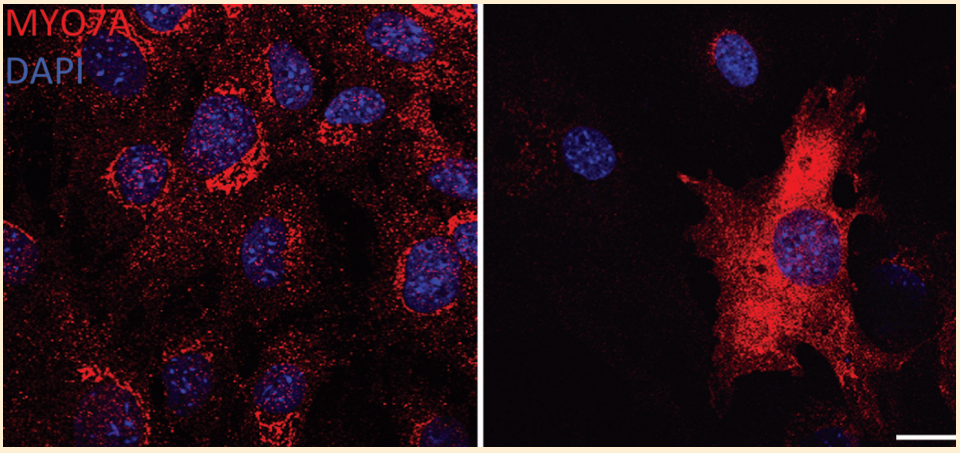
Primary Cell Lines a Boon to Research

The safety of the needle biopsy for ocular melanoma patients has another significant implication—the subject of a third paper by Dr. McCannel's group. "Once you access part of the tumor tissue from biopsy, which is something that has never been done before, you can use that tissue for research," Dr. McCannel says. In the February 2011 issue of the journal *Molecular Vision*, her group reported the first well-characterized primary cell lines, cultivated in Dr. McCannel's laboratory, that are a true representation of the patient's ocular tumor. "This is truly a breakthrough for detailed studies and drug testing. We are the first to grow tumor cells that express the most critical mutations felt to drive this cancer from patients," Dr. McCannel explains.

The paper characterizes, in molecular detail, three cell lines that Dr. McCannel's group developed by culturing material taken from ocular melanoma patients who went on to develop metastasis. "While cell lines from primary melanomas have been grown from tissue taken from eyes that have been removed from patients, these cell lines are believed to have significant shortcomings for studying questions such as what drugs might help ocular melanoma patients," Dr. McCannel says. "The cell lines grown from *in vivo* tissue pave the way for more revealing studies of the biology of metastatic ocular melanoma, including research to understand the pathways that lead to metastasis." Dr. McCannel and colleagues have established a collaborative effort with MD Anderson Cancer Center in Houston to conduct high-throughput testing and proteomics research in an effort to discover drugs and pathways that could be effective in treating the disease, and to gain a better grasp of the metastatic process.

"We are excited and hopeful that our discoveries will help to improve the way ocular melanoma patients are managed," Dr. McCannel says. "We see a significant opportunity to make headway in both sight-saving and life-saving treatments for patients."

Gene Therapy Delivery for Usher 1B *continued from cover*



Myosin VIIa (MYO7A) is detected by immunofluorescence (red) in primary cultures of RPE cells, following treatment with an adeno-associated virus carrying the MYO7A gene (AAV2-MYO7A). Despite its large size, the MYO7A gene can be accommodated by AAV2 virus and thus delivered to the cells.

Left: Cells were treated with virus that had been given full-length MYO7A to package. Normal levels and distribution of MYO7A are observed.

Right: Cells were treated with two populations of virus, each packaging overlapping halves of the MYO7A gene. Only a small minority of cells were able to generate full-length MYO7A from this treatment, and those that did typically showed pathological overexpression. Nuclei are stained blue. Scale bar = 10 um

approach," says David S. Williams, PhD, director of the Stein Eye Institute's Photoreceptor/Retinal Pigment Epithelial (RPE) Cell Biology Laboratory. The findings of Dr. Williams' group were made primarily by postdoctoral fellow Vanda Lopes, PhD, and were reported in the January 24, 2013, issue of the journal *Gene Therapy*.

One of the challenges to developing gene therapy for Usher 1B has been finding a way to successfully deliver the affected gene to retinal cells—the photoreceptor cells and the RPE cells. A series of clinical trials first published in 2008 showed that adeno-associated virus (AAV) is effective in transporting the *RPE65* gene to the eyes of patients with another retinal disease, LCA. As a vector, AAV also carries significant advantages. According to Dr. Williams, the most significant advantage is that it does not integrate

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AARP The Magazine ranks Jules Stein Eye Institute as No. 3 in the country for complex eye-care referrals.

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into the genome, and thus does not risk disrupting other genes. "The photoreceptor and RPE cells don't divide anymore when they're in the adult eye, so the effects of a non-integrating virus can be long-lasting—in fact, the *RPE65* gene that is delivered by AAV appears to last for life," Dr. Williams explains.

These advantages and the proven success of AAV in transporting the *RPE65* gene to the eye raised the question of whether AAV might also be able to be used to deliver *MYO7A*, the Usher 1B gene. However, AAV is a relatively small virus, and it had been thought that it could package only genes smaller than 5 kb; the Usher 1B gene is 7 kb. But in their study, Dr. Williams and colleagues showed that in using AAV as a vector with the large *MYO7A* gene, they could correct the mutant phenotypes in a mouse model of Usher 1B. "This is a major boon," Dr. Williams says. "It indicates that despite the fact that these AAV viruses have a small packaging capacity, somehow they are able to deliver the gene." Dr. Williams says that research by other groups points to a possible explanation: "Essentially the virus chops up the gene, and the RPE and photoreceptor cells are able to put the pieces back together after delivery."

Dr. Williams points out that patients with Usher syndrome are well suited for gene therapy because, due to their deafness and now current genotyping, they are readily identifiable at birth, before there is any change in the retina. "Gene therapy is not a cure once the disease has started; it's a preventive therapy," Dr. Williams explains.

"What's encouraging is that the AAV has already been used so successfully for the LCA clinical trial," he adds. "Our findings mean that the successful LCA approach can also be used for retinal gene therapy involving large genes, such as the Usher 1B gene, and potentially for other retinal degenerations caused by defects in large genes."

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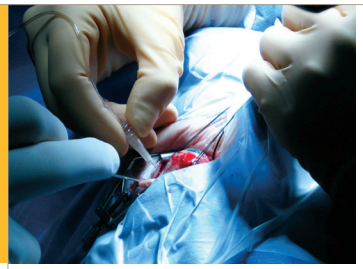

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