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Perspective

Proceedings of the Association for Research in Vision and Ophthalmology and Champalimaud Foundation Ocular Oncogenesis and Oncology Conference

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The 2018 Ocular Oncogenesis and Oncology Conference was held through a partnership of the Association for Research in Vision and Ophthalmology (ARVO) and the Champalimaud Foundation. Twenty-one experts from international ocular oncology centers, from the Champalimaud Clinical Centre and the Champalimaud Foundation Cancer Research Program, and from patient advocacy organizations, delivered lectures on subjects that ranged from global ocular oncology, to basic research in mechanisms of ocular malignancy, to clinical research in ocular cancers, and to anticipated future developments in the area. The scientific program of the conference covered a broad range of ocular tumors—including uveal melanoma, retinoblastoma, ocular surface tumors, and adnexal and intraocular lymphomas—and pathogenesis and management were deliberated in the context of the broader systemic cancer discipline. In considering the latest basic and clinical research developments in ocular oncogenesis and oncology, and providing the opportunity for cross-talk between ocular cancer biologists, systemic cancer biologists, ocular oncologists, systemic oncologists, patients, and patient advocates, the forum generated new knowledge and novel insights for the field. This report summarizes the content of the invited talks at the 2018 ARVO-Champalimaud Foundation Ocular Oncogenesis and Oncology Conference.

Introduction

The Ocular Oncogenesis and Oncology Conference was held on July 18 to 21, 2018 at the Champalimaud Centre for the Unknown in Lisbon, Portugal, through a collaborative partnership between the Association for Research in Vision and Ophthalmology (ARVO) and the Champalimaud Foundation. The goal of this unique conference was to consider the latest basic and clinical research developments in ocular oncogenesis and oncology in the context of the systemic cancer field. In applying advances in systemic oncogenesis and oncology to the ocular field, the scientific program focused on malignant tumors of the eye, including uveal melanoma, retinoblastoma, ocular surface tumors, and adnexal and intraocular lymphomas. Topics that were covered included global perspectives in ocular oncology, research on oncogenic mechanisms, including genetic, immunologic, and basic cell and molecular biologic aspects, results of recent oncologic preclinical studies and clinical trials in diagnostics and therapies, and anticipated future progress toward improving outcomes in ocular cancer.

The conference included 21 invited talks, with opening and closing keynote lectures given by international experts in oncogenesis and oncology from ophthalmic oncology centers around the globe, from the Champalimaud Foundation, and from patient advocacy organizations. At the close of the meeting, participants uniformly agreed that the intermingling of knowledge, including divergent points of view, from basic scientists researching in oncogenesis, ocular oncologists practicing worldwide, clinicians researching and managing systemic cancer, and patients and patient advocates, had propelled the field forward. To share the knowledge that has been gained through the interactions of these distinct, but mutually informative, disciplines, this report summarizes the content of the invited talks delivered at the conference.

Global Perspectives in Ocular Oncology

Dr. Brenda Gallie described how retinoblastoma can become a "zero death" cancer. Outcomes for 8000 children newly diagnosed with retinoblastoma each year depend on where they are born: globally 70% die, but with resources and knowledge more than 95% survive.[1] The complexity of retinoblastoma confounds conventional clinical research. Multidisciplinary care requires hundreds of clinical encounters at multiple centers with unique medical records, impeding communication, and continuity of care. DEPICT HEALTH (previously called DePICT^{RB}) is a novel tool ready to address these needs and support quality research for retinoblastoma.[2] At each encounter clinical data are entered by caregivers and viewed by a patient-defined circle of care. The global network of retinoblastoma experts (1rbw.org) and patients (we-chope.org) has a long history of effective collaboration, and welcomes DEPICT HEALTH, which can (1) collect global patient data across The Cloud and provide patients immediate access to their health information, and (2) provide real-world data to generate real-world evidence and support the goal of zero deaths from retinoblastoma.

Dr. Rubens Belfort discussed the Brazilian model for addressing gaps in access to ocular oncology. He presented the challenges of offering ocular oncology care in Brazil and described new strategies, including the use of telemedicine and Internet-based teaching to both patients and general ophthalmologists. Brazil is a large country with 207 million people, and 70% of the population does not have medical insurance and depends on government-funded health care. For the past 8 years, his team has worked to improve ocular cancer outcomes by promoting early diagnosis and efficient care despite substantial financial constraints. He described the following initiatives: the mobile phone WhatsApp-based ocular oncology "second opinion" app, called "Oncophone"; YouTube-based ocular oncology videos for patients and ophthalmologists (www.cancerocular.com.br); the ocular oncology center in the Amazonian region; and some low-cost strategies for tumor treatment, including primary endoresection for uveal melanoma[3] and laser for conjunctival tumors.[4]

The work of Dr. Junyang Zhao in managing retinoblastoma in China illustrated how care for ocular tumors may be coordinated across a large population base. Starting in 2006, he and Dr. Gallie have collaborated to set up a network for the management of Chinese children with retinoblastoma. Today this network covers two-thirds of the country's 9.6 million–km^2 area and includes 29 centers. Dr. Zhao visits each center every few months, and he has adopted standard protocols in diagnosis, classification, treatment, and follow-up for every patient. He treats more than 300 new cases of retinoblastoma every year. He has documented the following

outcomes in his clinical practice: increased 5-year follow-up rate from 48% of cases of retinoblastoma (2006–2009) to more than 95% cases (2013–2016); decreased mortality from 21% to 5%; and increased eye-salvage rate from 20% to over 80% when vitrectomy and tumor resection are performed.[5,6]

The opening keynote lecture, entitled "Patient of the future–making use of a valuable resource," was delivered by Dr. Bettina Ryll. The ultimate beneficiaries of healthcare systems are patients. In times when demands for a more patient-centered care are accompanied by increasing constraints on resources, patients can provide unique experiential insights into diverse conditions, the desired and undesired effects of therapy, and the effectiveness of healthcare delivery. In that regard, patients probably represent the largest underused resource in our healthcare systems. However, leveraging this resource for improved healthcare decision-making will depend on accurately capturing and representing patient preferences in all their diversity and granularity, both between and within conditions. In a collaboration with the European Medicines Agency, the Melanoma Patient Network Europe (MPNE) has piloted methodology to capture risk–benefit preferences in different groups of its audience, and believes this is a possible way forward to treat and to decide on behalf of individuals rather than hypothetical averages.[7]

Basic Science Research on Ocular Oncogenesis

Taking a systemic perspective, Dr. Eduardo Moreno spoke on cell competition and cancer. Direct comparison of cell fitness in *Drosophila* species is used to detect and eliminate many types of viable, but impaired, cells to delay ageing and prevent developmental malformations. In humans, opportunities for fitness-based cell selection have also been described during development and cancer, but they normally rely on indirect competition for survival factors or nutrients, and whether a system dedicated to direct comparison of cell fitness is conserved in humans is unknown. His group has studied human Flower isoforms and found that expressing "Win" isoforms 2 and 4 gives cells a competitive advantage over those expressing "Lose" isoforms 1 and 3.[8] Lose-expressing cells are not culled if neighboring cells have similar levels of Lose, and therefore act as canonical fitness fingerprints. They have also found that human tumors benefit from fitness-based cell selection to gain competitive growth. These results illustrate how ancient mechanisms of cell recognition and selection are active in humans and impact oncogenic growth.[9,10]

Dr. Steffen Heegaard talked about basic mechanisms of conjunctival and orbital lymphoma. Lymphoma is the sixth most common type of cancer, with 20 cases per 100,000 persons per year in the Western World. Approximately 90% of lymphomas are of B-cell origin; 1% to 2% of these occur in the ocular region, and lymphoma is the most common malignant orbital tumor. Risk factors for developing lymphoma are inflammatory diseases, such Sjgren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, celiac disease, and autoimmune thyroiditis. Infectious pathogens known to cause lymphoma include the bacterium, *Helicobacter pylori*, and the viruses, hepatitis C virus, human herpes virus-8, Epstein-Barr virus, and human immunodeficiency virus. Little is known about why tumor lymphocytes settle down in a specific tissue. However, this process of "homing" is regulated by adhesion molecules and their interplay with chemokines in lymphoid tissue.[11] Extranodal marginal zone B-cell lymphomas are presumed to develop due to infection and inflammation causing cell damage, leading to an increase in reactive oxygen species, and if chromosomal instability develops, malignant transformation may occur.[12] Several chromosomal abnormalities associated with extranodal marginal zone B-cell lymphomas include trisomy 3, trisomy 18, and some chromosomal translocations (i.e., t[11;18] → API2-MALT1, t[14;18] → IGH-MALT1, t[1;14] → Bcl10-IGH, and t[3;14] → FoxP1-IGH). Most of these chromosomal changes lead to an abnormal activation of the transcription factor, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB).

Dr. Sarah Coupland gave an update on the basics of intraocular lymphoma. Primary vitreoretinal lymphoma is the most common intraocular lymphoma.[13] It is a high-grade typically B-cell malignancy, arising in the retina, and is often associated with central nervous system disease, and thereby a poor prognosis. This form of lymphoma must be distinguished from low-grade B-cell choroidal lymphoma, which does not disseminate to the brain and has a good prognosis, as well as from secondary ocular manifestations of systemic lymphomas. Vitreoretinal lymphoma often "masquerades" as another intraocular disease and therefore may be associated with diagnostic delay. Pathologic work-up includes cytomorphology and immunoprofiling with adjunctive tests, such as

cytokine analysis, polymerase chain reaction (PCR) for immunoglobulin gene rearrangements, *MYD88* mutational testing, and recently, bespoke next-generation sequencing panels.[14–16] Vitreoretinal lymphomas arise from activated postgerminal center cells, explaining their aggressive clinical course.[13]

Dr. Bruce Ksander discussed the pathogenesis of conjunctival and uveal melanomas. Skin and choroidal melanomas are clinically and genetically distinct tumors even though they both arise from the malignant transformation of normal melanocytes. The reason for this must reside, in part, in the differences between the function of melanocytes in skin and eye. The function of melanocytes in the skin has been studied extensively, while very little is known about the function of choroidal and conjunctival melanocytes. Skin and conjunctival melanomas share mutations that activate the mitogen-activated protein kinase (MAPK) pathway (i.e., *BRAF*, *NRAS*, *NF1* genes), indicating skin and conjunctival melanocytes acquire similar ultraviolet radiation–induced mutations. Improving the current treatment regimens for patients with conjunctival melanoma will require further studies on the mechanisms of tumor growth and dissemination using new animal models.[17,18] By contrast, uveal melanomas have mutations in genes encoding G-coupled protein receptors (i.e., *GNA11*, *GNAQ*) or mutations in genes that signal through Gα subunits (i.e., *CYSLTR2*, *PLCB4*). Other gene mutations (i.e., *BAP1*, *SF3B1*, *EF1AX*) are believed to have a cooperative role in determining the aggressiveness of tumor expansion.[19] A recent important new mouse uveal melanoma transgenic model confirms the contributions of *GNA11* and *BAP1* gene mutations in tumor growth, but also indicates our understanding of the genetic pathogenesis of uveal melanoma is not fully complete.[20] Development of new successful therapies for patients with uveal melanoma will depend upon understanding the function of normal ocular melanocytes and animal models that trigger their malignant transformation.

The immunology of ocular melanoma was addressed by Dr. Martine Jager. Uveal melanoma is the most common primary malignancy in the adult eye. Loss of chromosome 3 and gain of 8q, and somatic mutations in the *BAP1* gene, located on chromosome 3, are associated with an increased risk of developing metastases. Loss of BAP1 expression is associated with increased inflammation.[21] As immunotherapy is currently being developed for many malignancies, one might expect that inflamed uveal melanoma would be a readily druggable target. However, most studies on the clinical use of immune checkpoint inhibitors—including inhibitors of cytotoxic T cell lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1)—have not shown success with regard to the treatment of uveal melanoma metastases. These drugs may be more effective for conjunctival melanoma, a malignancy that is more similar to cutaneous melanoma.[22]

Dr. Hans Grossniklaus reflected on the Zimmerman effect as he described the mechanisms of metastatic uveal melanoma. In the 1970s, Zimmerman and colleagues noted that the peak in mortality for metastatic uveal melanoma was at approximately 2 to 3 years after enucleation of the eye with the melanoma; this has become known as the "Zimmerman effect." Zimmerman hypothesized that the act of enucleation spread tumor cells.[23] This, in part, led to the establishment of the Collaborative Ocular Melanoma Study (COMS). The COMS confirmed the Zimmerman effect, but disproved the Zimmerman hypothesis.[24] Dr. Grossniklaus' laboratory group and others have since found explanations for the Zimmerman effect. These include that there are random mutations in uveal melanoma, resulting in larger tumors giving rise to more metastases than smaller tumors, and that specific mutations are associated with peaks in uveal melanoma mortality at approximately 3 and 5 to 8 years after treatment.[25] Additionally, host immune and nonimmune factors account for emergence and growth of dormant uveal melanoma micrometastases in the liver over time.[26]

Clinical Research in Ocular Oncology

Using breast cancer as an example, Dr. Fatima Cardoso stressed the critical importance of working from bench to bedside in evaluating genomic and biomarker tests for clinical application.[27] At the bench, all potential testing requires technical validation. This necessitates confirmation of sensitivity, specificity, and reproducibility. Subsequently, the proposed test must be clinically validated by identifying meticulously phenotyped subsets of patients with cancer, who manifest significant differences in risks for relapse, and/or for response to precise therapies. She described the development of MammaPrint, a 70-gene genomic signature that is able to identify patients who have an excellent prognosis when treated with adjuvant endocrine therapy alone and in whom adjuvant chemotherapy may be safely omitted.[28]

Dr. Dan Gombos summarized the treatment of primary and metastatic uveal melanoma. In 2018, the diagnosis and management of uveal melanoma stands at a significant crossroad, with outstanding diagnostic accuracy and prognostication, yet limited improvements in patient survival.[29] Clinical features, combined with multimodal imaging, generally lead to an accurate diagnosis. Size, location, and histopathology facilitate in stratifying metastatic risk. Combined with DNA or RNA molecular assessment, those at highest risk for distant metastasis are easily identified.[30] Local treatment options, including brachytherapy or charged particle radiation, have improved and now allow globe preservation in all but the most advanced cases. Experimental approaches using laser-stimulated viral plasmids are under investigation. Following ocular therapy, a personalized surveillance regimen targets those at highest risk of metastasis with greatest frequency. Current survival rates are not improving, however, although new immune and targeted therapies may be sound platforms for adjuvant therapies that target metastasis. Identifying high-risk patients and enrolling them in well-designed prospective clinical trials is the next critical step toward curing this malignancy.[31]

Dr. Swathi Kaliki reported the latest in the management of ocular surface squamous neoplasia. The gold standard method of diagnosis of this squamous neoplasia is histopathology, and standard management is with wide excisional biopsy, respecting 3- to 4-mm tumor-free margins, followed by double freeze-thaw cryotherapy to the surgical margins and ocular surface reconstruction. However, in the recent times, the neoplasia may be diagnosed using the noninvasive technique of high-resolution optical coherence tomography (OCT), and various nonsurgical techniques have emerged for optimal management, including topical mitomycin C (MMC), 5-fluorouracil (5-FU), and interferon-alpha 2b (IFN-α2b).[32] The tumor regression rates of ocular surface squamous neoplasia with MMC, 5-FU, and IFN-α2b are comparable, while the side effects are minimal with IFN-α2b. In cases with giant neoplasia (i.e., >6 clock-hours of limbal involvement) not responding to medical treatment, surgical excision may lead to limbal stem cell deficiency in more than 50% of cases. Prophylactic concomitant simple limbal stem cell transplantation after surgical excision of giant ocular surface squamous neoplasia can prevent or minimize limbal stem cell deficiency.[33]

Old paradigms and new challenges of cancer and organ preservation were considered by Dr. Carlos Carvalho. In the last few decades, most patients with uveal melanoma and retinoblastoma have been successfully treated without surgical enucleation. The possibility of organ and function preservation in the tumors of the eye also applies to other solid tumor types (i.e., head and neck, esophagus, cervix, prostate, rectum, and anal canal) where radiotherapy and/or chemotherapy may be able to induce a complete "remission" and eventually avoid a surgical amputation.[34] To achieve organ preservation, the treatment must induce not only a transient remission, but a sustained complete response. This particular biology may depend not only on the tumor cell sensitivity to the treatment, but also on the interactions between the tumor and its microenvironment and particularly on an "adjuvant" effect that is mediated by the immune system. The characterization of the tumor–host individual immune profile may be the key to better understanding the biology of a complete response, and to open more doors, not only to better organ and function preservation, but also to new treatment strategies.[35,36]

Dr. Jasmine Francis described current treatment of retinoblastoma, focusing on ophthalmic artery chemotherapy and intravitreous chemotherapy. The main present-day treatment for retinoblastoma at her institution involves ophthalmic artery chemosurgery and intravitreous chemotherapy. Recent studies have covered various pertinent topics. Eyes that successfully complete ophthalmic artery chemosurgery may have recurrent disease, but the overall ocular survival rate is 96%; factors associated with reduced recurrence include an interval shorter than 4 weeks between infusions and over 50% of infusions delivered via the ophthalmic artery (in contrast to indirect routes).[37] Ophthalmic artery chemosurgery has a major impact on the outcome of patients with bilateral retinoblastoma, particularly on historically high ocular survival rates.[38] Combining ophthalmic artery chemosurgery with intravitreous chemotherapy results in a faster time to regression, less future recurrence, and more eyes saved.[39] The use of intravitreous chemotherapy expands beyond vitreous disease to the treatment of retinal, subretinal, and anterior chamber retinoblastoma with excellent ocular survival, and the majority of eyes retaining or gaining electroretinogram responses.[40]

Dr. Jacob Pe'er reviewed the current management of vitreoretinal lymphoma. The suspicion of vitreoretinal lymphoma is raised when ocular findings include vitreous cells, mainly in clumps, which is the most common finding, yellow-white retinal infiltrates, and subretinal or subretinal pigment epithelial infil-

trates by OCT. The diagnosis is usually made by vitreous biopsy analyzed by cytology, including immunocytopathology, which considered to be a gold standard, by PCR for molecular analysis for the *IGH* gene rearrangement and mutated *MYD88*, and by cytokine analysis mainly by measuring the interleukin (IL)-10:IL-6 ratio.[41] Cytokine levels in the anterior chamber and rarely chorioretinal biopsy also may be used. Results for a group of 150 patients at his clinical service indicate that in the associated laboratory, the IL-10:IL-6 ratio is more sensitive than cytology or PCR in the diagnosis of vitreoretinal lymphoma, leading to his recommendation that analysis of cytokine levels is a robust diagnostic tool in cases of suspected vitreoretinal lymphoma. Vitreoretinal lymphoma may be treated by radiation therapy, chemotherapy using systemic, intrathecal, and intravitreal routes, and biological therapy using rituximab. For over 20 years, his clinic has used only intravitreal injection of methotrexate—administering (400 μg) per injection and giving 25 injections over 1 year, as one injection twice per week for 1 month, one injection per week for 2 months, and one injection per month for 9 months[42]—to treat 122 eyes of 74 patients, including 48 binocular cases. All patients responded fully after two to 16 injections. Tumor recurred in only two eyes, and these were treated successfully with a full second course of methotrexate. Side effects were mostly superficial and temporary. The group has concluded that intravitreal chemotherapy with methotrexate is a highly effective treatment for vitreoretinal lymphoma.

Looking to the Future Management of Ocular Cancer

Dr. Markus Maeurer presented immune surgery as a possible approach for patients with uveal melanoma. The advent of immune therapies has extended our view of cancer therapy—from focusing on tumor cell biology to the wider angle of a complex tumor ecosystem with diverse immune cell subsets interacting with evolving tumor cell populations—at different anatomic sites and at different timepoints during the treatment process. A number of highly effective cellular therapies have been developed, targeting overexpressed tumor-associated antigens and common mutations as well as the patients' personal 'mutanome', associated with the antigen processing and presentation machinery.[43,44] In contrast to the situation of cutaneous melanoma, major histocompatibility complex (MHC) class I loss in primary uveal melanoma appears to be associated with improved survival. Detailed mapping of the determinants of immune failure and immune fitness in the tumor ecosystem will be key to developing targeted approaches that provide biologically and clinically meaningful, 'tailored' cellular products for therapy, dependent on MHC expression in primary or metastatic uveal melanoma lesions.

Ocular complications of new oncologic treatments were discussed by Dr. Arun Singh. The rapid advancements in the field of oncology have resulted in the transition from cytotoxic chemotherapeutic agents to molecularly targeted therapies. The complexity of cellular pathways creates challenges for designing therapeutic agents that do not overlap with the physiologic activities of the normal human tissues. Distinct patterns of adverse effects related to the molecularly targeted therapies have emerged with their increased clinical usage. Molecularly targeted agents act through a variety of mechanisms, which result in side effects related to a specific agent. Most ocular tissues are susceptible, with effects on periocular skin, the ocular surface, neurosensory retina, and central visual pathways.[45] The majority of ocular toxicities reported are mild and nonspecific (i.e., conjunctivitis, epiphora, and visual disturbances); severe blinding complications are rare.[46,47] Given the complexity of the clinical setting in which targeted therapies are used, a multidisciplinary approach for management is required.

Dr. Jose Pulido spoke on the hamartia of checkpoint inhibitors and the emergence of viroimmunotherapy for uveal melanomas. Recent use of immunotherapy with checkpoint inhibitors has made a major impact on the progression-free and overall survival in patients with many solid cancers, including cutaneous melanoma.[48] The efficacy is closely related to the number of mutations per megabase, with the higher number having the greater efficacy.[49] Unfortunately, uveal melanomas have the lowest number of mutations per megabase of solid cancers studied, and consequently the worst response to checkpoint inhibitors of any solid cancer. There are many differences between cancer cells and normal cells. The most well-known difference is the increase in glycolysis in cancer cells, causing the Warberg effect and the ability of positron emission tomographic scans to visualize tumors.[50] Another difference is that some cancer cells are more susceptible to viral infection because they are replicating and because they do not respond to interferons. Oncolytic virotherapy involves preferentially infecting growing

cancer cells with virus.[51] However, a challenge in this therapy is that all cancer cells must be infected. Viroimmunotherapy uses viruses to trigger an immune response.[52] It involves infecting a cancer with virus, and with epitope spread, to generate an immune response directed against virus-infected cancer cells that subsequently targets all cancer cells. Dr. Pulido's team showed vesicular stomatitis virus (VSV) with a prostate cancer DNA library was active against prostate cancer in a mouse model, but had no effect in a mouse melanoma model; conversely, VSV with a melanoma DNA library had promoted survival of mice with melanoma, but not mice with prostate cancer.[53] They also showed that three tumor-expressed antigens, not an entire DNA library, was necessary for therapeutic effect.[54] Present work aims at a clinical trial of VSV expressing an interferon to augment the difference between cancer and normal cells, plus a tumor antigen, for metastatic melanoma.

Dr. Laurence Desjardins talked about the future in the management of ocular tumors, drawing on her experiences at the French Institut Curie. Here, the ocular oncology service has been taking a conservative approach to the management of uveal melanoma since the early 1980s. Between 300 and 350 new patients are evaluated each year, and management involves proton beam therapy, iodine plaque brachytherapy, enucleation for large tumors, and fine needle biopsy for prognostication; each year 60 to 80 patients present with metastatic disease. A prospective database with clinical information from more than 8000 patients, a collection of primary and liver metastasis samples, and a serologic collection is housed here. The service has been responsible for the French national database since 2008, and it coordinates the French national network for uveal melanoma care (MELACHONAT).[55] The prognosis of patients with metastatic disease is still poor despite efforts to test new drugs for this disease. Two years ago, Institut Curie and three other centers (i.e., Leiden University, University of Liverpool, and Jagiellonian University), plus two biomedical companies and the patient association, MPNE, came together as the UM CURE 2020 Project, to increase research on uveal melanoma. The Champalimaud Foundation and Seeding Science also participate in this project. The consortium's goals are to develop a European biobank, preclinical evaluation of biology-driven therapeutic approaches, next generation preclinical models of uveal melanoma, characterization of metastatic disease, identification of novel targets, and clinical trials.

Dr. Richard Carvajal delivered the closing keynote lecture, entitled "A new optimism: uveal melanoma in the era of precision oncology and immuno-oncology." The field of oncology has borne witness to remarkable progress over the past 15 years in the realms of both precision medicine and immuno-oncology. The successful application of both precision oncology and immuno-oncology for the treatment of cutaneous melanoma has resulted our ability to achieve prolonged disease control and cures in over 30% of individuals with metastatic disease. While similar progress has not yet been achieved in the uveal melanoma field, the successes achieved in cutaneous melanoma provide cause for renewed optimism. While the clinical results of agents targeting activated signaling pathways downstream of GNAQ, GNA11, PLCB4, and CYSLTR2 for the treatment of advanced uveal melanoma have been disappointing to date,[56,57] novel therapeutic strategies addressing epigenetic aberrations in uveal melanoma have demonstrated promise preclinically, and now are being pursued in early phase clinical trials of bromodomain inhibitors and other epigenetic modifying agents.[58,59] In parallel, although to date clinical trials evaluating the efficacy of immunologic checkpoint blockade in this disease have not demonstrated significant activity, other immunologic treatment strategies, including adoptive T cell therapy and T cell redirection, have shown promising early clinical results, with IMCgp100, a T cell redirection therapy, now in registration intent clinical trials (Carvajal R, et al. *IOVS* 2018;59:ARVO E-Abstract 3622).[36] Thus, our rapidly developing understanding of the underlying biology and immunobiology of uveal melanoma is leading to a new generation of novel therapies, which hold great promise in providing meaningful improvement in the lives of our patients with advanced disease.

Conclusions

The 2018 ARVO-Champalimaud Foundation Ocular Oncogenesis and Oncology Conference was the first-of-its-kind, bringing together multiple professional and patient groups with a common interest in improving outcomes for patients with ocular tumors. Interactions between the different groups resulted in valuable exchange of concepts across knowledge bases. As one example, ocular oncologists learned from systemic oncologists that receptor status of a cancer may change following metastasis, introducing the concept of restaging when approaching a metastatic ocular disease. As another example, ocular and systemic oncologists acknowledged they

would be a team working toward treating uveal melanoma with tumor-infiltrating lymphocytes sourced from metastatic lesions. Separately, the concept of the mutanome brought basic scientists and clinicians together in thinking about personalized treatment regimens for individual patients with ocular cancers. There was also recognition that oncogenic pathways overlap between uveal and cutaneous melanomas, which should provide for future cross-pollination in the development of biological inhibitor therapies. Importantly, ocular and systemic oncologists learned that patients and patient advocates differ substantially in their respective desires for knowledge of pathology and treatment, which has important implications for trial design, as well as clinical management. These interactions at the 2018 ARVO-Champalimaud Foundation Ocular Oncogenesis and Oncology Conference highlighted the value of cross-disciplinary meetings involving basic, translational, and clinical researchers, working within and outside the eye field, as well as patient groups.

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