We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

154

Countries delivered to

Our authors are among the

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

CLARIVATE ANALYTICS

BOOK CITATION INDEX

INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Introductory Chapter: Current and Future Trends in the Diagnosis and Management of Uveitis

Alejandro Rodriguez-Garcia and C. Stephen Foster

1. Introduction

Uveitis represents a significant burden of visual loss causing around 10–15% of all cases of blindness in the United States, and it is the fifth cause of visual loss in the developed world, accounting for up to 20% of legal blindness [1]. Visual loss due to uveitis currently has a significant impact on the productivity and quality of life of many patients worldwide. Therefore, advances in research and development of diagnostic techniques and therapeutic strategies are crucial for patients suffering from many forms of infectious and autoimmune intraocular inflammation.

One of the main obstacles that ophthalmologists face on diagnosis and treatment of eye disease is the unique complexity of the physical and physiological barriers, as well as the delicate anatomical structures of the human eye. This biologic scenario, particularly in highly destructive tissue disorders like infectious and autoimmune uveitis, represents a challenge for early and accurate diagnosis and effective therapy. Even today, with all possible diagnostic resources available in tertiary eye care facilities, more than 30% of patients suffering from uveitis do not have a definitive etiologic diagnosis [2]. The same is true for current therapeutic methods which suffer from lack of specificity, and are limited to availability at the site of inflammation due to the complex anatomical and physiological characteristics of the eye [3]. Therefore, the development of improved diagnostic methods and therapeutic modalities for inflammatory ocular disorders has recently received special and intense attention by the uveitis research community.

2. Advances in diagnosis of uveitis

In the past decades, scientific research at the molecular level and technological development have revolutionized medicine like never before. Such advances, particularly those related to detection technology are significant since early, and accurate diagnosis allows prompt and adequate treatment. Molecular biology has revolutionized medicine with the promise of improving our understanding of the pathogenic mechanisms that produce disease. The human plasma proteome has become the primary target for molecular analysis directed to improve the diagnosis and monitor the therapeutic response of many systemic and ocular disorders. There are at least eight different classes of plasma proteins classified by designed and functional basis. Two such groups are: the "tissue leakage products," which are intracellular proteins that are released into the plasma due to cell damage or death; and the "foreign proteins," which come from infectious microorganisms or parasites

and are released or exposed to the plasma are the main, but not the only source for diagnostic assays. The plasma proteome has been typically analyzed by electrophoresis combined with chromatography and mass spectrometry [4]. However, many new diagnostic methods have emerged, like DNA microarrays, which may be used for disease diagnosis by detecting biomarkers (genotyping, post-translational modifications, multi-SNPs marker screening, and determination of disease-relevant genes); detecting infectious agents (bacteria, virus, and fungal detection); and genetic disorders (detection of chromosome abnormalities, mutation analysis, and screening of SNPs) [5]. This methodology may interact with other molecular detection methods to study different disease biomarkers from blood, saliva, and other body tissues and fluids like aqueous and vitreous humors. For example, the ability to measure a wide range of molecular components in saliva and compare them to the plasma proteome has become a feasible way to study immunologic markers and microbes for autoimmune and infectious diseases, respectively [6]. Another application of molecular tools like polymerase chain reaction (PCR) has improved the timing for confirmatory diagnosis of infectious uveitis and endophthalmitis [7]. However, the number and type of microorganisms that may be studied in a given sample is limited due to differences in amplification techniques, as well as primers and fluorescent labels availability on multiplex detection systems. More recently, the use of next-generation sequencing (NGS) has proven to be a promising diagnostic strategy for multiple detections of common and rare microorganisms, including virus associated with infectious uveitis and endophthalmitis present in single vitreous samples. An important contribution of NGS so far is related to the improvement of pathogen detection in cases of negative culture endophthalmitis [8].

Despite these promising advances, the development and implementation of many new diagnostic techniques still need to be assessed for their effectiveness regarding precision and accuracy; sensitivity and specificity; predictive value, and cost-benefit balance convenience to be standardized and used widely on a clinical basis.

Imaging diagnostic methods have also suffered significant improvement. The development of the ocular coherence tomography (OCT) which provides non-contact, *in vivo*, cross-sectional, high-speed, and high-resolution images of different ocular structures including the cornea, anterior segment, retina, and optic nerve has evolved from low resolution time-domain image acquisition technology, to spectral domain and swept-source high-definition OCT with en-face, more in-depth, and extended image acquisition modalities [9]. Another significant advancement in diagnostic imaging technology is the development of multimodal devices, which allow the use of different complementary imaging techniques like fluorescein and indocyanine green digital angiography, wide-field angiography, autofluorescence, OCT, and OCT-Angiography all-in-one single machine [10]. Such multimodal equipment has permitted saving costs, time, office space, and less personal rotation when performing multiple studies to a single patient.

Another innovative and very exciting development in ocular image analysis has to do with artificial intelligence (AI), a new field of computer science research that will dramatically change the diagnostic and therapeutic pathways of many chronic degenerative ocular conditions including uveitis. Artificial intelligence already permits early identification of diabetic retinopathy, glaucoma, age-related macular degeneration, retinopathy of prematurity, refractive errors, and cardiovascular risk factors based on color fundus photographs through deep learning algorithms [11]. Very soon, patients will routinely be taken a non-mydriatic fundus photograph at the pre-exam room by an ophthalmic technician allowing the accurate recognition of many systemic associated and primary ocular disorders. Image pattern recognition is the basis of this technology, which requires

a large number of fundus photographs to learn from (training dataset) as well as a separate database for validation (validation dataset) [12]. This technology may be coupled with imaging diagnostic devices, such as a fundus camera with fluorescein, indocyanine green, and autofluorescence capabilities; SD-OCT, swept soured OCT, OCT-A, corneal topography, visual system aberrometry and wavefront imaging, anterior segment tomography, and ultrasound, among others, for the detection of specific diagnoses. Soon, this technology will be applied to patients with different forms of uveitis with specific and characteristic clinical appearance analyzed by different image diagnostic devices that will permit the accurate computerized diagnosis in a routine exam.

3. Advances in therapy of uveitis

Topical therapy with eye drops makes up more than 90% of ophthalmic formulations including different corticosteroids and non-steroidal anti-inflammatory eye drops. However, their intraocular bioavailability is limited by tear clearance, nasolacrimal drainage, and limited penetration related to the anterior biological barriers including the corneal epithelium and the hemato-aqueous barrier. Moreover, protein binding and enzymatic degradation also account for the limited absorption into target tissues [13]. Many different drug delivery strategies, including prodrugs, chemical permeability enhancers, stimuli-responsive *in situ* gels, and drug delivery carriers like liposomes are being developed to counter the elimination mechanisms mentioned before [14]. The emergence of nanotechnology has impulse the development of such therapeutic strategies for many ocular diseases including uveitis. Different active drugs have been coupled with nanocarriers to overcome the ocular anatomic barriers for direct interaction with specific intraocular tissues, increasing their therapeutic efficiency. Drugs loaded into nanoparticles improve their pharmacodynamics and pharmacokinetics and at the same time, reduce their immunogenicity, biorecognition, and toxicity [15]. One of the most developed fields in ophthalmic pharmacology is the sustained-release intraocular drug delivery devices. Polymeric-controlled release microparticle injections and implants, cyclodextrin-based nanospheres, nanocapsules, microencapsulated cells, liposomes, nano-micelles, and dendrimers are among the most used methods to deliver anti-inflammatory and immunomodulatory drugs into the eye [15, 16]. Such strategies are intended to avoid the side effects of prolonged systemic corticosteroids and immunosuppressive chemotherapy. An intraocular injection may provide a high-dose of medication directly into the site of inflammation with few or no systemic side effects. However, this therapeutic approach is not exempt from potential serious complications like endophthalmitis, vitreous hemorrhage, and retinal detachment, particularly when the administration needs to be repeated several times to achieve their purpose [17]. So far, several polymeric implants are already being used for the control of intraocular inflammation, including corticosteroid formulations [18]. Many other nanotechnology carriers mentioned before may be coupled with different drugs like cyclosporine-A, ganciclovir, non-steroidal anti-inflammatory drugs, anti-angiogenic, and anti-glaucoma medications to be delivered intraocularly. However, because nanoparticles are recently developed, they face several challenges including the need for extensive *in vivo* studies in animal models and then in humans to validate their efficacy and safety. Another essential task is the identification of specific ocular disease-related biomarkers and their cellular and molecular function to develop target-specific drugs that block the biomarker function.

More recently, transscleral iontophoresis has been employed to deliver sufficient dose medications into the eye in a non-invasive way, avoiding injections or the implantation of sustained-release drug devices with minimal side effects [19].

On the other hand, many specific, target-directed biologic molecules manufactured by recombinant DNA technology are used for treating joint systemic and ocular autoimmune inflammation. Such molecules consist of monoclonal antibodies, soluble receptors, cytokines, natural cytokine antagonists, and accessory molecules in antigen presentation. They play critical roles in the pathogenesis of inflammatory uveitis, like TNF-α, IL-1, IL-6; IL-17, T, and B-lymphocytes; and adhesion molecules like LFA-1 and ICAM-1 [20].

Future therapeutic strategies that may be exploited include immune tolerance, inducers of apoptosis, neuroprotective agents, gene therapy, gene transcription factors, and other modulating molecules that permit reprogramming of cells *in vivo*.

Author details

Alejandro Rodriguez-Garcia[1*] and C. Stephen Foster[2]

1 Tecnologico de Monterrey, School of Medicine and Health Sciences, Institute of Ophthalmology and Visual Sciences, Monterrey, Mexico

2 Massachusetts Eye Research and Surgery Institute, Ocular Immunology and Uveitis Foundation, Harvard Medical School, Boston, MA, USA

*Address all correspondence to: arodri@tec.mx

IntechOpen

References

[1] Durrani OM. Degree, duration, and causes of visual loss in uveitis. British Journal of Ophthalmology. 2004;**88**(9):1159-1162. DOI: 10.1136/bjo.2003.037226

[2] Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. American Journal of Ophthalmology. 2005;**140**(3):509-516

[3] Loftsson T, Sigurdsson HH, Konradsdottir F, Gisladdottir S, Jansook P, Stefansson E. Topical drug delivery to the posterior segment of the eye: Anatomical and physiological considerations. Die Pharmazie - An International Journal of Pharmaceutical Sciences. 2008;**63**(3):171-179. DOI: 10.1691/ph.2008.7322

[4] Anderson NL, Anderson NG. The human plasma proteome. Molecular and Cellular Proteomics. 2002;**1**(11):845-867. DOI: 10.1074/mcp.R200007-MCP200

[5] Yoo SM, Choi JH, Lee SY, Yoo NC. Applications of DNA microarray in disease diagnostics. Journal of Microbiology and Biotechnology. 2008;**19**(7):635-646. DOI: 10.4014/jmb.0803.226

[6] Streckfus CF, Bigler LR. Saliva as a diagnostic fluid. Oral Diseases. 2002;**8**:69-76

[7] Chiquet C, Lina G, Benito Y, Cornut PL, Etienne J, Romanet JP, et al. Polymerase chain identification in aqueous humor of patients with postoperative endophthalmitis. Journal of Cataract and Refractive Surgery. 2007;**33**(4):635-641. DOI: 10.1016/j.jcrs.2006.12.017

[8] Deshmukh D, Joseph J, Chakrabarti M, Sharma S, Jayasudha R, Sama KC, et al. New insights into culture negative endophthalmitis by unbiased next generation sequencing. Scientific Reports. 2019;**9**(1):844. DOI: 10.1038/s41598-018-37502-w

[9] Invernizzi A, Cozzi M, Staurenghi G. Optical coherence tomography and optical coherence tomography angiography in uveitis: A review. Clinical and Experimental Ophthalmology. 2019;**47**(3):357-371. DOI: 10.1111/ceo.13470

[10] Nagiel A, Lalane RA, Sadda SR, Schwartz SD. Ultra-widefield fundus imaging: A review of clinical applications and future trends. Retina. 2016;**36**(4):660-678. DOI: 10.1097/IAE.0000000000000937

[11] Ting D, Cheung C, Lim G, Tan G, Jama NQ. Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations. Journal of the American Medical Association. 2017;**318**(22):2211-2223. DOI: 10.1001/jama.2017.18152

[12] Hogarty DT, Mackey DA, Hewitt AW. Current state and future prospects of artificial intelligence in ophthalmology: A review. Clinical and Experimental Ophthalmology. 2018;**47**(1):128-139. DOI: 10.1111/ceo.13381

[13] Bisht R, Mandal A, Jaiswal JK, Rupenthal ID. Nanocarrier mediated retinal drug delivery: Overcoming ocular barriers to treat posterior eye diseases. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2018;**10**(2):e1473. DOI: 10.1002/wnan.1473

[14] Ye T, Yuan K, Zhang W, Song S, Chen F, Yang X, et al. Prodrugs

incorporated into nanotechnology-based drug delivery systems for possible improvement in bioavailability of ocular drugs delivery. Asian Journal of Pharmaceutical Sciences. 2013;**8**(4):207-217. DOI: 10.1016/j.ajps.2013.09.002

[15] Weng Y, Liu J, Jin S, Guo W, Liang X, Hu Z. Nanotechnology-based strategies for treatment of ocular disease. Acta Pharmaceutica Sinica B. 2017;**7**(3):281-291. DOI: 10.1016/j.apsb.2016.09.001

[16] Al-Halafi AM. Nanocarriers of nanotechnology in retinal diseases. Saudi Journal of Ophthalmology. 2014;**28**(4):304-309. DOI: 10.1016/j.sjopt.2014.02.009

[17] Avery RL, Bakri SJ, Blumenkranz MS, Brucker AJ, Cunningham ET Jr, D'Amico DJ, et al. Intravitreal injection technique and monitoring: Updated guidelines of an expert panel. Retina. 2014;**34**(Suppl. 12):S1-S18. DOI: 10.1097/IAE.0000000000000399

[18] Pavesio C, Zierhut M, Bairi K, Comstock TL, Usner DW, Group FAS. Evaluation of an intravitreal fluocinolone acetonide implant versus standard systemic therapy in noninfectious posterior uveitis. Ophthalmology. 2010;**117**(3):567.e1-575. e1. DOI: 10.1016/j.ophtha.2009.11.027

[19] Hastings MS, Li SK, Miller DJ, Bernstein PS, Mufson D. Visulex: Advancing iontophoresis for effective noninvasive back-to-the-eye therapeutics. Drug Delivery Technology. 2004;**4**:53-57

[20] Sharma SM, Fu DJ, Xue K. A review of the landscape of targeted immunomodulatory therapies for non-infectious uveitis. Ophthalmology and therapy. 2018;**7**(1):1-17. DOI: 10.1007/s40123-017-0115-5