AN OVERVIEW OF OCULAR TOXICITY MODELS

Ocular toxicity can be broadly classified into two types – toxicity resulting from direct exposure of the corneal layer to a drug or stimulus and toxicity caused by systemic administration of a test article. Toxicity studies are a key requirement for the approval of any ophthalmic drug. Till date, over 50 drugs have been approved for various ophthalmic diseases[1] and the most recent approval was for Vabysmo to treat wet AMD (age-related macular degeneration) and diabetic macular edema[2]. The pace of drug development in the ocular space is likely to continue and every therapy that has the potential to move into clinical trials requires comprehensive toxicology testing.

Animal models have been the mainstay of ocular toxicity testing for several decades and the models of choice have been rabbits, rats and in some cases nonhuman primates[3]. Rabbit models have been widely used as the eye is large and easily accessible but there is increased interest in reducing animal use in ocular toxicity due to ethical concerns. One example is the growing global ban on using animals for cosmetics testing. The European regulation (EC) No. 1223/2009 has been a key driver and, in the US, the Humane Cosmetic Act is in the legislative process. There is increased interest in using *ex vivo* and *in vitro* based methods to test drug modalities for ocular toxicity. One example of an *ex vivo* organotypic model is the use of isolated rabbit eyes to directly test the toxic impact of new therapies[4]. The advantage of using isolated organotypic models is that the whole eye or just the corneal tissues is that they can be obtained from animals used for other drug testing or slaughterhouse waste[4]. Additionally, the *ex vivo* tissues can be extensively analyzed for toxicity using histopathology and imaging methods. It is interesting to note that apart from isolated eye tissues, ocular toxicity can be measured in non-ocular models such as the chorioallantoic membrane vascular assay (CAMVA) that uses a membrane on fertilized chicken eggs as a surrogate for the eye conjunctiva[4]. The development of cell-based assays is of increasing interest but early iterations of *in vitro* tests have limited applications. For example, the EYTEX™ system uses a synthetic mix of lipids and proteins to reconstitute a membrane disc that mimics the ocular membrane. However, this assay has very limited translational potential. There is a clear need for advanced cell-based models and one such example is the development of retina pigmented epithelia (RPE) assays to assess ocular toxicity[5]. The RPE is a layer of pigmented cells that face the retina and form a tight barrier between the retina and vasculature. Therefore, an RPE cell-based model has predictive potential to measure retinal damage from systematically administered drugs but development and validation studies are required for regulatory acceptance and wide scale adoption.

Therapies that target eye diseases require extensive ocular toxicity studies but it is important to note that therapies for other diseases should also be evaluated for ocular toxicity. For example, it is well known that several oncology therapies have known ocular side effects[6]. In most cases, the therapies cause temporary damage which is reversed upon the completion of the therapeutic regimen. However, in some cases, ocular damage is irreversible. One case study was published several years ago where an oncology small molecule inhibitor was shown to cause ocular toxicity at high doses in a canine model[7]. The drug target was hsp90, a chaperone protein that is required for oncogenic kinase activity. While the small molecule inhibitor showed efficacy against tumors, it caused irreversible eye damage at high doses resulting in the termination of the drug development program[7].

Based on the requirement of ocular toxicity for all novel mono and combination therapies, and the interest in reducing animal model use, there is a strong impetus to develop physiologically relevant cell-based models to test ophthalmic therapies as well as systemically administered oncology therapies.

References:

1. https://www.centerwatch.com/directories/1067-fda-approved-drugs/topic/104-ophthalmology
2. https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-vabysmo
3. https://www.sciencedirect.com/science/article/abs/pii/B9780124171442000287
4. https://www.sciencedirect.com/science/article/pii/S0300483X14002157
5. https://nc3rs.org.uk/crackit/vitro-platform-retinal-toxicity-assessment-and-disease-modelling
6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10478646/
7. https://journals.sagepub.com/doi/10.1177/1091581813484500