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Ocular melanin modulates pharmacokinetics and drug disposition of therapeutic agents

Viral Kansara, John Reilly, Cornelia Forster, Ann Brown, Jakal Amin, Timothy Drew and **Bruce Jaffee**
Novartis Institutes for Biomedical Research, USA

Melanin is a heterogeneous biopolymer which is present in the front and back of the eye. Due to its acidic and hydrophobic nature, many therapeutic agents bind to melanin-rich ocular tissues such as the iris-ciliary body, choroid and retinal pigment epithelium of the eye. We hypothesized that drugs with high affinity to melanin are linked to higher ocular exposure, with melanin postulated to be a potential depot for such compounds. To test this hypothesis, *in vivo* ocular and plasma pharmacokinetic (PK) studies of three compounds with high, medium and low melanin affinity were performed in pigmented and non-pigmented rats. Male Sprague-Dawley (non-pigmented) and Brown-Norway (pigmented) rats were used to determine ocular and plasma PK of selected compounds. The PK parameters were determined using Watson LIMS (Non-compartmental analysis). Using a high-throughput chromatography based *in vitro* assay, we screened 306 compounds of diverse chemical structures for their in vitro melanin affinity (67 – low-; 168 – medium-; 71 – high- affinity). In our *in vivo* studies, a significant increase in ocular exposures of high affinity (AUCPEC: 73μM*h vs. 2μM*h; AUCretina: 8 μM*h vs. 3μM*h) and medium affinity (AUCPEC: 9μM*h vs. 0.6μM*h; AUCretina: 6μM*h vs. 2.6μM*h) compounds were observed in pigmented rats compared with non-pigmented rats. The increased ocular exposure (*in vivo*) correlated with increased retention time on the chromatography (in vitro) method. This vitro assay wasshown to be predictive of in vivo melanin dependent ocular compound deposition. This approach provided excellent *in-vitro-in-vivo* correlations(IVIVC). In conclusion, this research suggests that ocular melanin affinity modulates ocular PK and drug retention in the eye, and may influence the pharmacological action of ocular targeted therapeutic agents.

Biography

Viral Kansara is the Investigator at the Novartis Institutes for Biomedical Research. He leads Ocular Pharmacokinetics and Drug Delivery laboratory within Pharmacology group. His team focuses on discovery and development of novel targets and delivery systems to treat AMD, diabetic retinopathy and glaucoma. Viralearned his Ph.D. in the field of Pharmaceutical Sciences from Ashim Mitra's Laboratory at the University of Missouri-Kansas City. He has authored 2 book chapters and numerous research articles in reputed journals and has been serving as a reviewer for *PharmRe*s, IOVS, AAPS *PharmSciTech*, and *JOPT*.

viral.kansara@novartis.com