

## Smart Therapeutic Delivery Platforms for Ocular Disorders/Diseases

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### Introduction

The increasing attention on ocular disorders/diseases is attributable to the projected increase in incidence for the next decade considering the increase in aging population worldwide. Also, majority of people will accord urgent medical attention to cases of visual impairment since vision is considered the most important sense in humans. However, there are many challenges that confront clinical management of ocular disorders/diseases which include: (a) the need for life-long drug application for chronic ocular disorders which places so much weight of treatment outcome on patient adherence; (b) poor drug access to the eyes from topical and systemic routes of administration; (c) erratic drug delivery and retention within the ocular tissues resulting in unpredictable therapeutic outcomes; and (d) limited knowledge on biocompatibility, safety and tolerability of most delivery systems in ocular tissues. For all the aforementioned points, it is widely accepted that development of clinically viable ocular delivery systems is an unmet need [1,2].

In this age of smart technology, new generation delivery systems (smart therapeutic delivery platforms) hold great promise for ocular applications with the capability of controlling drug delivery in response to various stimuli such as pH, temperature, and light [3-4]. Smart delivery systems can potentially offer great benefits over traditional systems since release of active/diagnostic agents can be controlled based on disease-specific (locally available; proximal) or non-disease specific (external; remote) stimuli. The opportunity to tailor drug availability (at the site of action) to the progression of ocular disease is worthy of note. However, a major concern for systems that rely on proximal stimuli (disease-associated) is that levels of the triggers can vary widely from patient to patient and even within the same patient at different times of the day or stages of the disease. Thus, clinical development of delivery systems that depend on proximal stimuli may be impacted by poor reproducibility.

We are of the opinion that photo responsive delivery systems are the most natural fit for ocular diseases/disorders since they can potentially exploit the normal exposure and reaction of the eye to light. Another main attraction is that spatial and temporal release of therapeutic payload in the ocular tissues can be achieved through remote activation [5-8]. In general, delivery systems that operate by remote activation are less prone to patient- or disease-dependent factors since activation can be precisely controlled through manipulation of wavelength, intensity and duration of light irradiation. Focusing on light-responsive delivery systems, the construct is such that appropriate responsive moieties are conjugated into polymeric/delivery materials so as to trigger photon-induced structural and/or property changes. Although, so much progress has been made over the years particularly in discovering new chromophores, there are major gaps that must be filled for practical (clinical) applications. For instance, the biodegradability and biocompatibility of most chromophores and polymeric units is a major barrier. Also, the nature and type of light trigger is another determinant of clinical viability. It is also noteworthy that most effective photoreactions require high energy photons such as short wavelength ultraviolet (UV) light as the trigger [9].

Application of UV-light as a trigger is not attractive clinically

since UV light is detrimental to tissues and is genotoxic. In addition, UV light has very limited tissue penetration depth due to extensive absorption and scattering by many components of biological systems. It was suggested that the detrimental effects on healthy cells/tissues can be curtailed by reducing the dose of UV light that is applied as the trigger [10]. But mere dose reduction is not a tenable solution, which prompted other investigators to consider strategies of avoiding UV-light activated systems in favor of systems that operate on longer wavelength lights such as near-infrared (NIR) or infrared (IR) lights which are safer than UV-light and can penetrate deeper in tissues. In the approach, NIR-responsive chromophores are conjugated on polymer backbone to achieve NIR-light responsiveness. However, the approach is plagued by the observation that most photoreactions involving NIR-responsive chromophores are generally very slow and require longer irradiation times. It is envisioned that the field of photoresponsive ocular delivery will benefit greatly from recent advancements in laser technology and processes that are driven by two photon absorption and photon-up conversion whereby irradiation can be achieved using safe and clinically acceptable photons or lasers that are clinically acceptable.

Over-all, the clinical viability of photo responsive ocular delivery systems will be dependent on a number of factors; which include: (i) safety and biocompatibility of the delivery platforms and light triggers; (ii) ease of elimination of photo degraded by-product of delivery matrix (from ocular tissues) after release of therapeutic payloads; (iii) patient acceptance of the delivery platform and method of administration; (iv) the delivery platform and the light trigger should not interfere with vision nor induce inflammation; (v) sensitivity of the delivery platforms to the light trigger must be coveted since it dictates irradiation times; and (vi) the ability to achieve reproducible photo responsive release of therapeutic payloads within the desired ocular tissues.

### Acknowledgement

The support from NEOMED is appreciated. Author does not have personal and/or financial conflict of interest.

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Received August 31, 2013; Accepted September 01, 2013; Published September 05, 2013

Citation: Oyewumi MO (2013) Smart Therapeutic Delivery Platforms for Ocular Disorders/Diseases. *J Biomol Res Ther* 2: e115. doi:10.4172/2167-7956.1000e115

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