Novel drug delivery systems for posterior eye diseases

Whitney Shatz
Genentech Inc., USA

Statement of the Problem: Age-related macular degeneration is an eye disease affecting the back of the eye which gradually destroys sharp central vision [1], and has the potential to greatly impact quality of life [2]. Intravitreal injection is the preferred route for ocular drug delivery of protein therapeutics, where maximal benefit is achieved with dosing every 4-8 weeks [3]. Less frequent dosing would reduce treatment burden and increase patient compliance [4], highlighting the need for long-acting delivery (LAD) technologies.

Methodology and Theoretical Orientation: Since clearance from the eye is governed primarily by diffusion [5], therapeutic Fab was chemically conjugated to various multivalent scaffolds via maleimide chemistry to increase Fab half-life. Each Fab-conjugate candidate was assessed based on a multitude of criterial including conjugation efficiency, ratio of Fab to carrier, hydrodynamic radius, long terms stability, viscosity and activity (Figure 1). In some cases, *in vivo* tolerability experiments were performed to assess biocompatibility with ocular tissues.

Findings: Evaluation of each system revealed attributes desirable for ocular LAD. Scaffolds composed of either PEG, HPMA or lipoprotein were effective in increasing Fab RH. Geometry did not greatly influence RH but had an impact on viscosity. Biocompatibility study demonstrated tolerability of PEG but not of lipoprotein carrier.

Conclusion and Significance: Though RH measurements *in vitro* are useful for predicting vitreal half-life [6], scaffold biocompatibility is more complicated and has remained a major hurdle to the success of novel technologies.

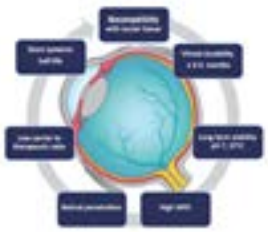

Figure 1. Many facets to consider in ocular LAD.

Recent Publications

1. van Lookeren Campagne M, LeCouter J, Yaspan BL, Ye W. Mechanisms of age-related macular degeneration and therapeutic opportunities. The Journal of Pathology. John Wiley & Sons, Ltd; 2014 Jan;232:151–164.
2. National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, Committee on Public Health Approaches to Reduce Vision Impairment and Promote Eye Health, Welp A, Woodbury RB, McCoy MA, Teutsch SM. Making Eye Health a Population Health Imperative: Vision for Tomorrow. Teutsch SM, McCoy MA, Woodbury RB, Welp A, editors. Washington (DC): National Academies Press (US); 2016 Sep.

3. Shatz W, Aaronson J, Yohe S, Kelley RF, Kalia YN. Strategies for modifying drug residence time and ocular bioavailability to decrease treatment frequency for back of the eye diseases. Expert Opin Drug Deliv. Taylor & Francis; 2018 Dec;16:43–57.
4. Ehlken C, Helms M, Böhringer D, Agostini HT, Stahl A. Association of treatment adherence with real-life VA outcomes in AMD, DME, and BRVO patients. OPTH. Dove Press; 2018;Volume 12:13–20.
5. del Amo EM, Rimpelä A-K, Heikkinen E, Kari OK, Ramsay E, Lajunen T, Schmitt M, Pelkonen L, Bhattacharya M, Richardson D, Subrizi A, Turunen T, Reinisalo M, Itkonen J, Toropainen E, Casteleijn M, Kidron H, Antopolsky M, Vellonen K-S, Ruponen M, Urtti A. Pharmacokinetic aspects of retinal drug delivery. Prog Retin Eye Res. Elsevier Ltd; 2017 Mar;57:134–185.
6. Shatz W, Hass PE, Mathieu M, Kim HS, Leach K, Zhou M, Crawford Y, Shen A, Wang K, Chang DP, Maia M, Crowell SR, Dickmann L, Scheer JM, Kelley RF. Contribution of Antibody Hydrodynamic Size to Vitreal Clearance Revealed through Rabbit Studies Using a Species-Matched Fab. Mol. Pharmaceutics. 2016 Sep;13:2996–3003.

Biography

Whitney Shatz received her M.S. in Biochemistry and Molecular Biology from the University of California in Santa Barbara, characterizing bacterial enzymes involved in the epigenetic process of DNA methylation. Since 2007, she has worked within the research organization at Genentech, supporting production and characterization of large molecule biologics. During her 11-year tenure, she has made significant contributions to the investigation of structure activity/relationship in antibody-dependent cell cytotoxicity (ADCC), as well as to the advancement of novel bispecific antibodies in a variety of disease areas. More recently, her focus has shifted to the development and characterization of protein-polymer bioconjugates for long-acting drug delivery. In addition, since 2016 she has been concurrently pursuing a doctorate in Pharmaceutical Sciences at the University of Geneva.

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