Protein based pharmaceutical formulations for ophthalmological applications

**Project Leaders:** Robert Gurny and Constantin J. Pournaras

**Project Members:** Marieke Veurink, Cinzia Stella and Cyrus Tabatabay

**Keywords:** ophthalmology; monoclonal antibodies; field flow fractionation; anti-inflammatory drugs

Age-related macular degeneration (AMD) is caused by the overproduction of new blood vessels with increased permeability and fragility within the macula. This process is initiated by over expression of vascular endothelial growth factor (VEGF) and the binding to its receptors VEGFR-1 and VEGFR-2. In order to prevent the formation of leaking blood vessels, monoclonal VEGF antibodies and their fragments are used as they bind with high affinity to VEGF and inhibit binding of VEGF to its receptors.

Since possible interactions between the anti-inflammatory drug and Avastin or Lucentis could cause instability of the proteins, we started our investigation by testing the stability of these combinations in vitro.

We measured the aggregation state of Avastin and Lucentis alone, and in combination with dexamethasone and triamcinolone, by multi-angle light scattering (MALS) after separation by asymmetrical flow-field-flow fractionation (FFF). FFF has the ability to separate proteins and particles according to their molecular weight without an interacting stationary phase and under much lower pressures than in conventional chromatographic methods.

Our results show that the combination with anti-inflammatory drugs does not decrease the stability of Avastin nor Lucentis based ophthalmic formulations. Further research will focus on the optimization of combined formulations and their effects in vivo.

There is an increasing interest in using these antibodies and their fragments for AMD therapy. Currently on the market are Lucentis® (Ranibizumab), an antibody fragment that is worldwide approved for the treatment of AMD, and Avastin® (Bevacizumab), an antibody registered for cancer therapy that is widely used off-label for this application.

Both drugs show improvement in visual acuity in clinical studies, but a disadvantage is that they have to be injected intraocularly every month, for up to one year. Because of patient discomfort and risk of complications, a reduced frequency in injections would be favourable.

The combination of Avastin and Lucentis with anti-inflammatory drugs like dexamethasone and triamcinolone could be a major advantage in optimizing the treatment of AMD and in prolonging the interval between two injections. Concomitant administration could lead to synergistic effects, since anti-inflammatory drugs are also known for their beneficial properties in the treatment of AMD.

Contact Information:
School of Pharmaceutical Sciences
Laboratory of Pharmaceutics and Biopharmaceutics
30, Quai Ernest Ansermet
CH-1211 Geneva
Switzerland

e-mail: Robert.Gurny@unige.ch
Tel: +41 22 379 6146 Fax: +41 22 379 6567