opn2EXPERTS - Half-life extension for biologics against retinopathies

Using novel types of biotherapeutics or functional assays, how would you propose to extend or validate the intravitreal half-life and retinal penetration of biologics?

Answers to this question including a proposal for collaboration can only be considered if they arrive no later than November 7, 2022 11:59 pm PST.

What is the context of the problem that we would like to solve?

Retinopathies, including age-related macular degeneration (AMD) and diabetic retinopathy (DR), are among the major causes for impaired vision and eventual blindness. Globally, more than 190 million individuals are affected by AMD and 93 million people are suffering with diabetic retinopathy.[1,2] Retinopathies are characterized by damage to the retina which can stem from several different causes including damage to blood vessels or macular cells.

Intravitreal drug delivery is the preferred route of administration for biologics intended to treat these retinopathies[3]. However, injection into the eye is associated with the risk of intraocular infection or inflammation and represents a high burden for the patient. Thus, injection frequency is of great importance. In order to ease this burden, our aim is to increase the time interval between two injections, i.e., to decrease injection frequency.

The vitreal half-life determines the injection frequency and it is known that the size of a molecule is a key parameter for the vitreal half-life. Larger molecules, which diffuse more slowly through the vitreous body, are known to have longer vitreal half-lives than smaller molecules.

While a large size can increase the half-life in the vitreous, it can also restrict penetration into tissues. Penetration into the retina is required for most therapeutics to reach their site of action (target). Molecule size may hinder drug candidates from penetrating through the inner limiting membrane into the retina and further into deeper layers of the retina.

However, optimization of the molecular size is limited and therefore additional mechanisms for extending the half-life are required. The challenge is to find alternative approaches, e. g. new types of biotherapeutics, extending the vitreal half-life of proteins on the one hand and allowing the drug to penetrate well into the retina on the other hand.

To identify a new approach, many molecules will need to be screened to identify optimal properties. To screen these molecules, one important requirement is to develop *in vitro* or *ex vivo* assays that are predictive for vitreal half-life and retinal penetration. *In vivo* testing is not feasible for a large number of drug candidates, and so relying on *in vivo* proof of concept alone will not allow for successful candidate progression.

Therefore, as part of this opn2EXPERTS question two related, but independent solution approaches are in scope:

First, we are looking for novel biotherapeutics approaches to enable both intravitreal half-life extension and increased retinal penetration of biotherapeutic molecules. Secondly, we are seeking innovative functional assay models to assess and validate the half-life extension and retinal penetration of biologics. Proposals that address either one of these two or both objectives would be in scope and eligible for a scientific review through our expert jury.

What potential solutions could be in scope?

1. Any novel, molecular approach that extends the vitreal half-life and increases retinal penetration of biologics. Covering, but not limited to the following ideas
    - Novel types of antibody/protein fusions (molecular formats)
    - Antibodies/binders to antigens facilitating ivt half-life extension or retinal penetration
    - Chemical modification of biologics, etc.
2. In addition, any innovative functional approach that allows analyzing intravitreal half-life extension and retinal penetration of biotherapeutic molecules, such as

- Predictive *in vitro* and *ex vivo* assay systems or multi-cellular or 3D tissue based assays, or
- biomechanical systems.

3. Suggested models need to have conceptual link to treat human retinopathies.

What potential solutions would be out of scope?

The following will be considered out of scope:

- Conventional approaches to extend half-life and retinal penetration of biologics that are based on pegylation or similar technologies.
- Proposals focusing exclusively on device technologies
- Proposals that focus exclusively on formulation approaches
- Proposals that represent *in vivo* models, assays, or methods suited solely for small molecules
- Proposals focusing on gene therapies

What benefits do we offer to you in exchange for having submitted a solution?

If your project is selected, you will have the opportunity to directly collaborate with the Biotherapeutics Discovery and Retinopathy Research teams of Boehringer Ingelheim and tap into their experience in the fields of biologics molecule discovery, biologics engineering, retinopathies, pharmacokinetics and -dynamics. In addition, you can expect appropriate funding for the prospective collaboration period. Your exact funding request should be outlined in your proposal. As a framework, we suggest that your initial funding request is structured in milestone and does not exceed 200,000 euros per submitted project in total.

Our collaboration agreement will provide full transparency about each partner's rights & obligations (including intellectual property rights). As part of the agreement, you will be encouraged to publish following the collaboration agreement (to be negotiated in good faith).

To maintain the highest degree possible in an open innovation environment, we plan to announce the winner(s) publicly and feature them on opnMe.com and our social media channels.

What are the key success criteria on which we base our selection for the best answer?

We are seeking research collaboration proposals that contain:

- A well-structured proposal outlining a new and compelling scientific approach.
- Outlining of the technical feasibility, and potentially existing data or previous publications that support feasibility / experience with outlined technology, based on existing techniques and established assays.
- Your exact funding request should be outlined in your proposal based on a well-thought-through project. The project should be structured in milestones and planned with key decision points (clear Go/No-Go criteria). The funding request for the initial milestones resulting in a Go/No-Go decision should not exceed 200,000 euros per submitted project in total.
- Proven track record in the required field of expertise.
- Ability to implement the outlined solution as part of a scientific collaboration project with Boehringer Ingelheim including access to a laboratory.

What information should be included in your answer submission?

Please use our answer submission template to provide a 2-3 page non-confidential proposal (available for download on the following site).

If confidential data exists that would strengthen the proposal, please indicate that information is available to share under a Confidential Disclosure Agreement (CDA). If we find the non-confidential concept proposal sufficiently interesting, we will execute a CDA for confidential discussions.

Anticipated Project Phases or Project Plan

Phase 1	Please complete your submission by **November 7, 2022, 11:59 pm PST** at the very latest
Phase 2	Our review of all proposals will be completed by end of December 2022 or latest by mid of January 2023 and scientists will be informed after that.
Phase 3	Potential collaboration starting date in Q1/2023

Submitting a collaboration proposal

- Check the outline of the opn2EXPERTS "Half-life extension for biologics against retinopathies" question on opnMe.
- Alternatively, you may click the "Get Submission Template" banner to access the material transfer template.
- Follow the instructions to upload your submission document (requires login or registration).
- The upload allows you to attach additional application files if desired.
- You will be able to access your final submitted collaboration proposal in your personal dashboard and follow its review status.
- Please also visit the FAQ section on opnMe.com to learn more about our opn2EXPERTS program.

References

1. Apte R. S. Age-related macular degeneration *N Engl J Med* **2021**, 385(6):539-547. DOI: 10.1056/NEJMcp2102061, PubMed.
2. Yau J. W. Y., Rogers S. L., Kawasaki R., Lamoureux E. L., Kowalski J. W., Bek T., Chen S-J., Dekker J. M., Fletcher A., Grauslund J., Haffner S., Hamman R. F., Ikram M. K., Kayama T., Klein B. E. K., Klein R., Krishnaiah S., Mayurasakorn K., O'Hare J. P., Orchard T. J., Porta M., Rema M., Roy M. S., Sharma T., Shaw J., Taylor H., Tielsch J. M., Varma R., Wang J. J., Wang N., West S., Xu L., Yasuda M., Zhang X., Mitchell P., Wong T. Y. Meta-Analysis for Eye Disease (META-EYE) Study Group *Diabetes Care* **2012**, 35(3):556-64. DOI: 10.2337/dc11-1909, PubMed.
3. del Amo E. M., Rimpelä A., Heikkinen E., Kari O. K., Ramsay E., Lajunen T., Schmitt M., Pelkonen L., Bhattacharya M., Richardson S., Subrizi A., Turunen T. Pharmacokinetic aspects of retinal drug delivery *Prog Retin Eye Res* **2017**, 57:134-185. DOI: 10.1016/j.preteyeres.2016.12.001, PubMed.