# INTERVIEW WITH DR. MARCO TANGELDER:

## NEW DEVELOPMENTS IN THE CLINICAL DEVELOPMENT LANDSCAPE FOR OPHTHALMOLOGY

Dr. Marco Tangelder is a clinical epidemiologist with more than 20 years of academic, pharmaceutical and biotech industry experience, in thrombosis and hemostasis research, development of antithrombotic therapies for a broad range of indications, development of gene therapy for hemophilia, and ophthalmology.

Prior to joining Medpace in 2017, Dr. Tangelder held key roles in various biotechnology and pharmaceutical companies in which he was responsible for translational medicine, phase 1-4 clinical development programs and regulatory approvals. Specifically, Dr. Tangelder served at ThromboGenics where he contributed to the BLA and MAA submissions of ocriplasmin (Jetrea®) leading to approval for the treatment of symptomatic vitreomacular adhesion, and where he also developed clinical trials for diabetic retinopathy, diabetic macular edema, and metamorphopsia.

Most recently, prior to joining Medpace, Dr. Tangelder led at uniQure the clinical development of gene therapy for hemophilia and contributed to preclinical development and translational research of gene therapy constructs for various rare disease indications. Dr. Tangelder received both his medical degree and PhD at the University of Utrecht in the Netherlands and received his Master's in Pharmaceutical Medicine at the Karolinska Institute in Stockholm, Sweden.

Dr. Tangelder is dedicated at Medpace to serve clients with innovative pipelines in ophthalmology and contributes to their development of advanced therapy medicinal products (ATMP) in sight threatening eye diseases.

**Ophthalmology is a growing therapeutic area in clinical research with new and exciting developments occurring in the field, particularly in stem cell and gene cell therapies.**

### What does the development landscape in ophthalmology look like today?

Many academic institutes and biotech companies initiated the research and development of gene and other advanced medical therapies for severe ocular diseases leading to severe visual disability or blindness. Currently, many gene therapy products are being developed preclinically and evaluated in trials for hereditary or genetically linked severe ocular diseases like retinal dystrophies, achromatopsia, retinoschisis, choroideremia, and age-related macular degeneration. But also, other innovative approaches, not on DNA but on RNA level, like RNA editing with antisense oligonucleotides, are under development for Leber's congenital amaurosis and Usher syndrome.

The huge unmet medical need for these debilitating diseases is obvious. We are, after so many years of innovative research, at the point to develop advanced therapies in the eye clinic and actually bring sight-saving treatments to patients. At Medpace, we are contributing to this effort by collaborating with several biotech companies and academic institutes, conducting exciting and promising clinical development programs.

### Why is the eye an ideal target for gene therapy?

Gene therapy is most effective for monogenetic diseases, where a known single mutation causes the disease. In many of the severe inherited retinal diseases this is the case. A challenge of gene therapy is the construct of the product and effective delivery of the functional gene. Most clinically used constructs consist of an adeno-associated viral (AAV) vector that contains the gene and an organ specific promotor, to infect and transduct as many cells as needed for a sufficient transgene expression, resulting in sufficient protein production to be effective. Adeno-associated viruses are harmless and common, and many people have been infected in their lives, and as a result, developed antibodies against these viruses. Patients with antibodies that neutralize a specific AAV vector are not suitable for systemic treatment (such as by intravenous injection), with that particular gene therapy product; and the proportions of these patients are up 50%.

The eye is a small organ, and gene therapy for retinal diseases is delivered in the enclosed subretinal space in a very small amount. Because of this, the systemic exposure to the AAV vector is close to zero, and patients do not develop neutralizing antibodies. Another advantage of this is that the second eye can also be treated, unlike with systemic gene therapy, where a second treatment would lead to lack of effect due to the presence of neutralizing antibodies. The disadvantage of the eye as a target for gene therapy is that a surgical procedure, vitrectomy, is needed before injection of the gene therapy in the subretinal space.

### How does imaging play a key role in ophthalmology research and what should a Sponsor look for in a partner?

Imaging plays a major role in ophthalmic research and development, as this offers many non-invasive evaluation methods of ocular structures. This enables us to effectively assess deterioration of eye structures over time, but also changes after experimental treatments in clinical studies. Furthermore, these so called imaging or anatomical biomarkers are closely associated to functional vision outcomes, which is of course of ultimate importance to patients.

However, there are challenges as well, when it comes to the methodologies of applying imaging outcome assessments in clinical trial settings. For that reason, we closely collaborate with the Boston Image Reading Center (BIRC) at the New England Eye Center. BIRC provides interpretation support for all image modalities currently applied in ophthalmic clinical trials. This is of utmost importance for rapid, reliable, and reproducible image assessment by academic experts, because the aim of scientific research is to deliver valid and generalizable study results.

### What are some challenges, considerations and risks that are specific to these studies?

Gene therapy is nowadays considered to be safe by regulatory authorities like the FDA and EMA. The main challenge is to avoid an immune response to the AAV vector that delivers the gene into the cells. For this reason, patients are very closely monitored the first months after systemic treatment, and in case of an immune response treated with a corticosteroid like prednisone. We treat patients with a short course of corticosteroid that starts pre-operatively, to avoid an inflammatory or immune response.

Furthermore, the follow-up durations in clinical trials are very long – five to ten years. And in my opinion, ideally, it should be life-long. The reason for this is to be able to detect any long-term safety issues, which we have not seen yet. And, to monitor the sustainability of the trans-gene effect after the single treatment, which will hopefully be life-long. For these reasons, it is of utter importance to select the right patients, willing and able to comply with the burden of study protocols.

### What motivates you and your interest in clinical research – particularly in ophthalmology?

On a personal note, I have family and friends with severe eye diseases, and I had two vision-threatening eye diseases myself. Luckily these were adequately treated, and the preservation of my vision made me very aware of the huge importance of visional functioning in daily life and activities. All of this motivates me tremendously to contribute to the development of novel innovative sight-preserving treatments.

## MEDPACE SUPPORTS STEM CELL AND GENE CELL THERAPY RESEARCH

Medpace has been a pioneer in the clinical development of advanced therapies including stem cell and gene cell therapies. Medpace provides an experienced team of experts who take an active role in the field and are at the forefront of rapidly changing clinical and regulatory developments.

## FULL-SERVICE CLINICAL DEVELOPMENT

Medpace is a scientifically-driven, global, full-service clinical contract research organization (CRO) providing Phase I-IV clinical development services to the biotechnology, pharmaceutical and medical device industries. Medpace's mission is to accelerate the global development of safe and effective medical therapeutics through its high-science and disciplined operating approach that leverages local regulatory and deep therapeutic expertise across all major areas including oncology, cardiology, metabolic disease, endocrinology, central nervous system and anti-viral and anti-infective.



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