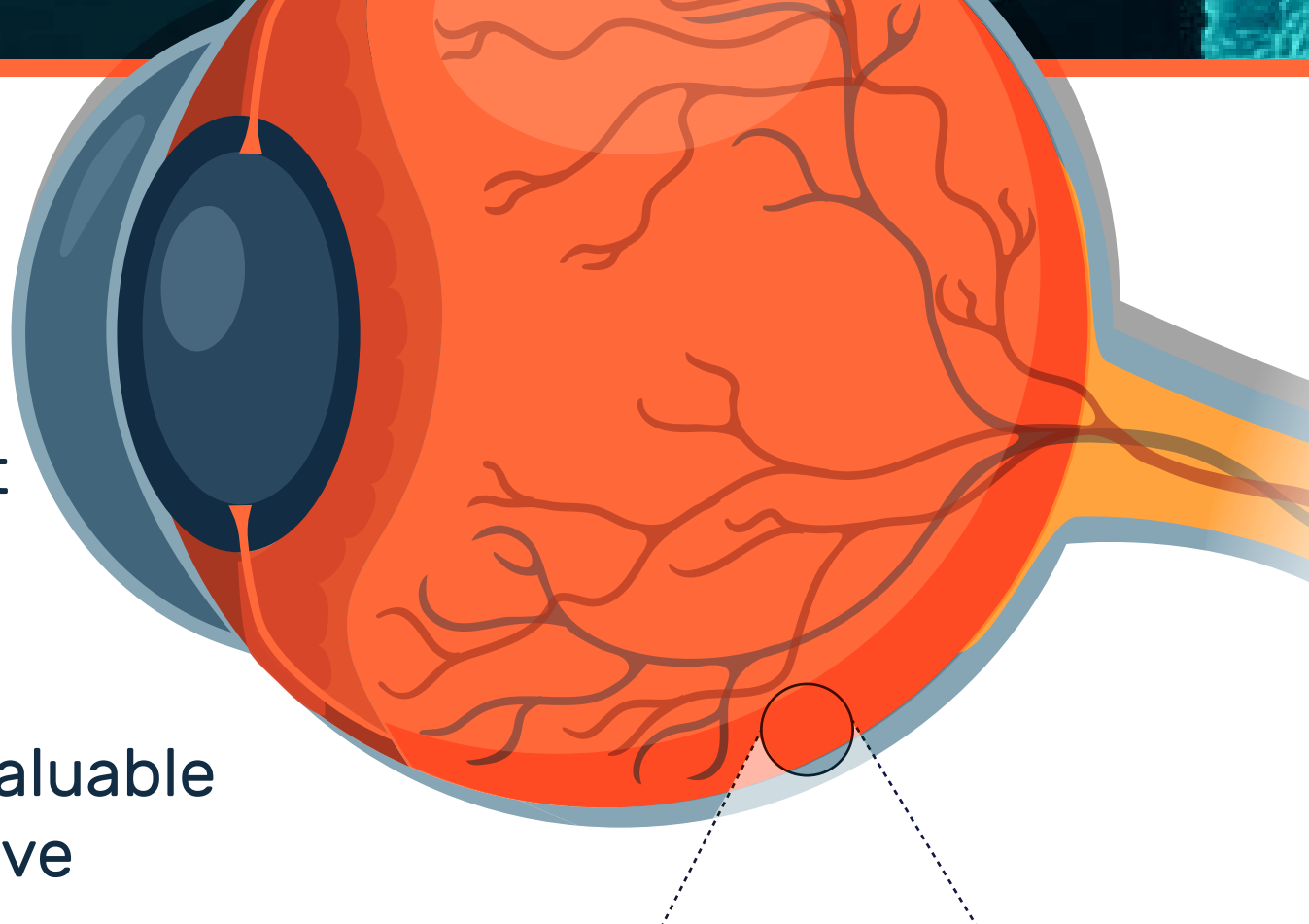
IN THE ZONE

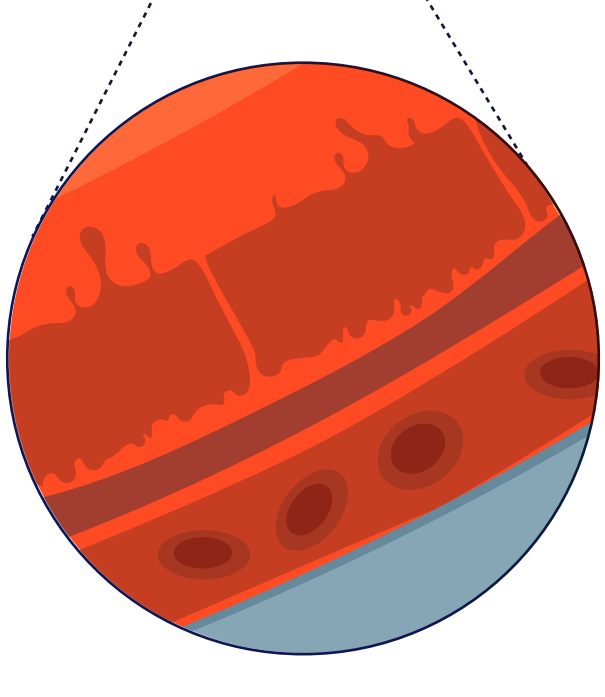
Ocular cell and gene therapies: why the eye?

Why the eye?



The eye has several properties that makes it an attractive target for cell and gene therapies, including:

1. **Vision** is considered the most valuable sense out of the five humans have
2. It is an **immune-privileged organ** due to the **blood–ocular barrier**



3. Compartmentalized anatomy is **easily accessible** and examined *in vivo* by ophthalmoscopy
4. The blood–retinal and blood–aqueous barriers **concentrate vectors** in the target area while **reducing systemic exposure**
5. The eye can be utilized for testing gene delivery for a **wide range of tissues** since it contains endothelium, epithelium, muscle and neuronal cells
6. The contralateral eye can act as an **experimental control**

Regulatory challenges of ocular CGTs

Novelty

CGTs are still an emerging therapeutic modality that lack a foundation of approved products to leverage when developing new therapies. Regulatory authorities must manage issues not previously reported in other regulatory procedures.

Safety

Determining safety in a preclinical setting is essential before first-in-human clinical trials. CGT products comprise unique considerations that must be unequivocally addressed.

Patient availability

Most CGT developers have focused on rare, genetic diseases in which gene replacement/editing has transformative potential. Accessing a large enough pool of patients for clinical trials may be challenging.

Regulatory change

Regulatory bodies are constantly adapting to provide guidance on safe market routes for gene therapies. Furthermore, within ocular gene therapies, the choice of the model and animal species for product safety evaluation can have a significant impact on the preclinical development timeline, either facilitating or delaying investigational new drug approval.

Manufacturing and scalability

Product quality, focusing on the production process definition and consistency will gain importance, as well as avoiding significant process changes during the product's development cycle and manufacturing capacity to account for similar properties of viral vectors and impurities.

Preclinical ocular CGTs

The nonclinical development path for ocular CGT products relies on three main pillars fully covered by Absorption Systems' capabilities:

Analytical release testing

In vivo studies

Bioanalytical testing

These three pillars involve conducting a sequence of exploratory studies to generate and provide information required for the investigational new drug application to enter clinical trials. These studies include the analytical characterization of the CGT product, the evaluation of the efficacy and safety profile (supported by *in vivo* studies and bioanalysis) and the development of a potency release assay allowing clinical batch release during the clinical stages of development.

Studies to conduct

Safety–toxicity studies

- Basic and advanced structural examination
- Basic and advanced functional evaluation
- Biodistribution

- Shedding
- Immunogenicity
- Tumorigenicity

Common platforms for CGT bioanalytics

- LBA (ELISA, MSD)
- Cell-based assays (transduction inhibition assay)
- Fluorescence-activated cell sorting
- Quantitative Western Blot
- Enzyme Activity Assays
- qPCr and ddPCR
- LC–MS/MS

Efficacy studies

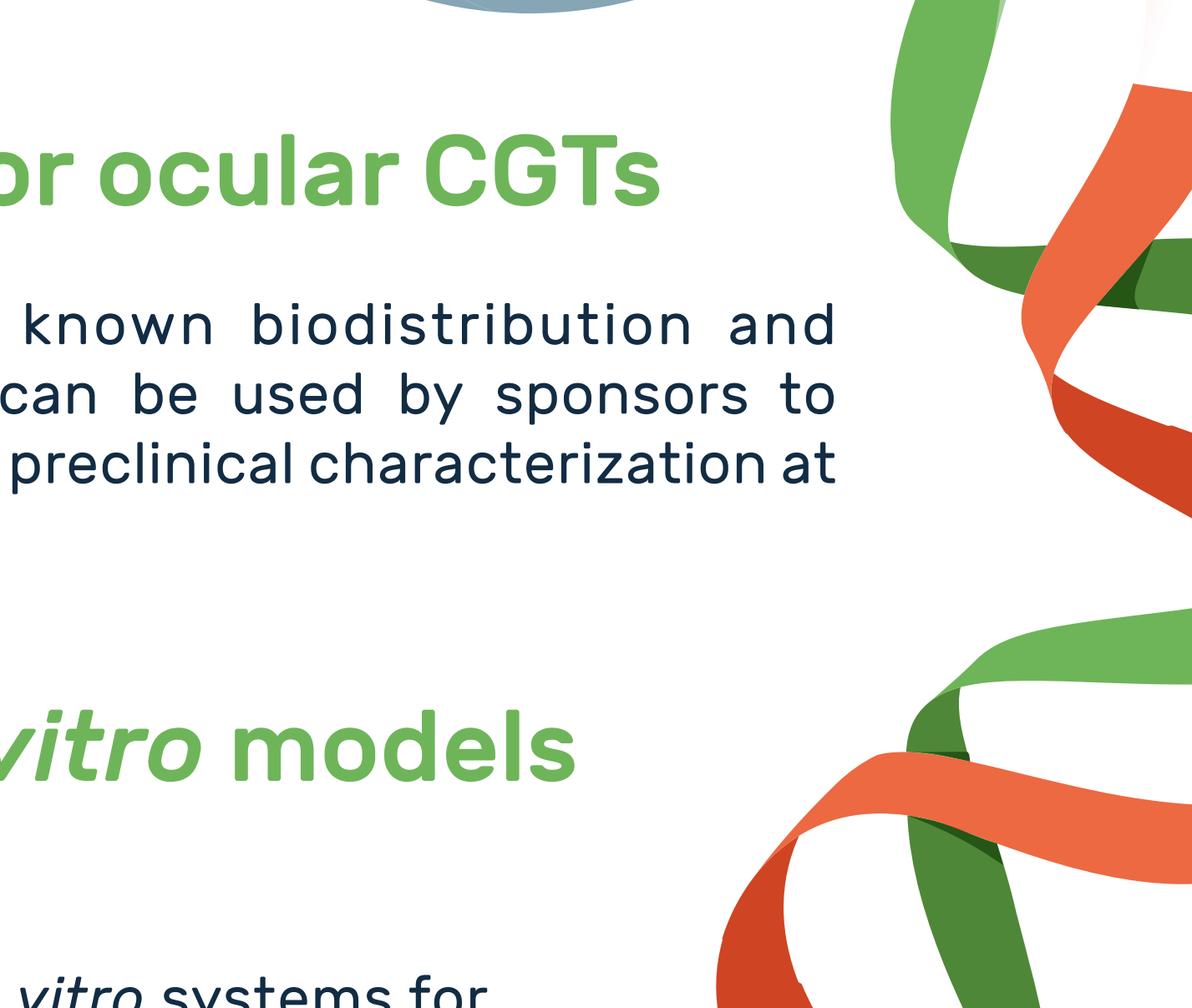
- *In vivo* efficacy studies
- Development of *in vitro* potency assay (also for batch release testing)

What does the future hold?

Increased focus on preclinical studies and how they can be utilized to maximize the possibilities of ocular CGTS and streamline approval will prove to be an emerging and dynamic area of interest. Continuing challenges for developing ocular CGTs include:

Better disease models

Most CGT products for rare inherited diseases use rodent disease models and move to more human-relevant species for GLP toxicology. Bridging the gap between these two types of animal models could improve clinical efficiency estimates, dose selection and phase trial design.



Bioequivalence for ocular CGTs

Standardized vectors with known biodistribution and toxicology are needed that can be used by sponsors to reduce the need for extensive preclinical characterization at the start.

Consensus on *in vitro* models of the eye

Finding standard models of *in vitro* systems for assessing CGT functionality will significantly enhance ocular CGT development and marketization strategies.

This infographic has been created as part of a Bioanalysis Zone feature in association with Absorption Systems