The Preclinical Process: Drugs Designed for the Back of the Eye

Preparation for preclinical stages of drug development could have implications for postmarketing success.

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For the past several years, Ora has worked with Retina Today *to craft articles for a column titled "Clinical Trials for the Retina Specialist" about the logistics of participating in and running a clinical trial. We have touched on several aspects of the clinical trial process, surveyed leaders in the industry, and hopefully served as a guide for retina specialists looking to get into the clinical research space. Moving forward, Ora will work on filling the column "Innovations in Retina" with articles that focus on innovations on the development side of the retina space, including novel technologies, business concepts and strategies, and product pipelines.*

A successful clinical trial depends on crucial decisions made during the preclinical stages of drug development. This includes, but is not limited to, preliminary pharmacology and toxicology testing, which contributes to selecting the best lead candidate for further development.

Animal models are extremely valuable in reproducing specific aspects of human diseases and are instrumental in studying disease mechanisms and testing therapeutic strategies.[1] It is important to match the mechanism of action of a drug candidate with a specific aspect of a disease process.

In animal models, researchers induce certain aspects of a potentially complex disease in an accelerated time frame, so it is important to keep in mind that it is not a total recapitulation of the human disease. This is particularly important for the retina because many posterior segment diseases occur at an advanced age in humans, a factor that is difficult to replicate in animal models.

Although translating preclinical to clinical success is never guaranteed, a carefully designed preclinical study paves the way for proper indication selection, thus increasing the chance that preclinical efficacy translates into a positive clinical outcome.

A BRIEF HISTORY OF ANIMAL MODELS: HEREDITARY TO TRANSGENIC

For many decades, basic research on both acquired and inherited retinal degeneration was based on a variety of animal models with disease origins from spontaneous mutations or environmental factors. In 1923, Clyde E. Keeler discovered a mouse strain lacking photoreceptors; he speculated that the animals carried an inherited defect in retinal development. He would go on to call these mice *r* (rodless retina).[2] In 1951, Bruckner and colleagues reported retinal degeneration in a strain of wild mice near Basel, Switzerland. These mice became known as *rd* (retinal degeneration) and would go on to become the most extensively studied animal model for human autosomal recessive retinitis pigmentosa (RP).[3] In 1993, 70 years after Keeler's original observations, it was discovered that the defects in the *r* mouse and the *rd* mouse were identical.[4] A number of hereditary retinal defects have also been identified in other animals, including other rodents, cats, dogs, and chickens.[1]

Innovation in genetic engineering has led to a rapidly growing number of transgenic animals and knockout lines mimicking the genetic origins of human retinal diseases. Mice and rats are among the most commonly used animals to date in the evaluation of specific drugs in animal models of human disease. However, other species, such as pigs, may also be useful for model development because their eyes are similar to the human eye in terms of anatomy, vasculature, and photoreceptor distribution.

STEPS IN PRECLINICAL DEVELOPMENT

Whether formulation efforts are underway for the evaluation of a new chemical entity or a compound is being repurposed for a new indication, certain criteria must be met in order to establish confidence to advance to the next step of the development process.

Target product profiles (TPPs) are tools that help to guide preclinical development. TPPs provide a framework to ensure that the preclinical program supports the intended clinical trial design and therapeutic use. A TPP will likely evolve as the drug development program progresses and should be continually reviewed by the team to assess whether it continues to align with the goals of the program.

The following is a general guide for the steps in the preclinical development process.

Step 1: Discovery

The discovery of novel drugs to treat retinal diseases often begins with target identification—that is, choosing a biochemical mechanism involved in a disease that affects the posterior segment. Potential drug candidates are then tested for their interaction with the drug target. This is often done through a series of in vitro enzymatic assays or binding studies followed by cell-based studies. Following careful review, a lead compound is chosen based on a confirmed interaction. Additional parameters that warrant careful evaluation include selectivity, potency, solubility, and stability. Compounds that show optimal performance in these tests are promoted to in vivo pharmacokinetic (PK) and efficacy studies.

Step 2: Formulation

Following the promotion of active compounds that satisfy preset criteria, a relevant research-level formulation must be developed to test active compounds in vivo. Drug formulation is often a considerable hurdle in ophthalmic drug development because it involves choosing all the correct ingredients to go along with the active drug itself. The importance of looking ahead to clinical trials at this phase of the drug development process cannot be emphasized enough.

What will ultimately come out of this preclinical work is an investigational new drug (IND) application, which must support the planned clinical trial design. (See Step 5, below.) Developers must devise a safe formulation that ensures the proper drug delivery parameters. At this stage of the process, the route of administration intended for the clinical trial should be clearly defined (topical, intravitreal, systemic, etc.). To that end, the choice of excipients should be carefully considered and only those known to be compatible with the desired mode of delivery should be used in the early non–good laboratory practice, or non-GLP, studies. Other considerations, such as the drug's stability in the formulation itself and for all the parameters involved with storage and shipment (heat, light, time, etc.) must also be determined.

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Step 3: Pharmacokinetics and Ocular Distribution

PK studies provide key information on drug dosage and frequency of administration. PK studies yield parameters including maximum concentration of the drug in the retina (C_{max}), time at which C_{max} is reached (T_{max}), and area under the curve (AUC) in order to characterize the body's effect on the drug. Because many potential drugs are eliminated from further development because of poor PK properties, many programs now incorporate PK screens early in the process to optimize the selection of successful candidates. Prior to animal efficacy studies, it is often advisable to conduct a PK and/or an ocular distribution study to confirm that the drug can reach the target tissue, and to provide data on dosage for use in efficacy models. PK studies carried out prior to the creation of an efficacy model should be performed in the same species as the anticipated efficacy model. Additional PK studies can be done later in development to better predict human exposure.

Step 4: Proof-of-Concept Study

One goal of a proof-of-concept study is to start defining what the ultimate clinical dose or dose range is going to be. The choice of the best animal model is based on the mechanism of action of the drug and the known pathology in the disease indication. The endpoints evaluated in the preclinical studies should mirror those that will ultimately be evaluated in humans in a clinical setting. In addition, benchmarking compounds and/or clinical comparators should be included, when possible, in the animal efficacy studies in order to increase translatability of preclinical success into clinical success.

Although clinical success is not guaranteed, careful and deliberate decision-making early in the process can provide a level of confidence in future success. An

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optimally formulated drug with an established PK profile contributes to an efficiently designed and interpretable animal efficacy study.

Step 5: Initiation of IND-enabling activities

Chemistry, manufacturing, and control efforts, also called CMC efforts, are the first step to initiating IND-enabling studies. The final clinical formulation must be optimized in order to ensure that it is stable, scalable, and can be made under good manufacturing practice conditions.

GLP toxicology studies are required by the US Food and Drug Administration (FDA) before a drug can be tested in humans. Toxicology studies also help the investigator understand the drug's behavior at the maximum dose level as well as at steady state, accumulation, and trough levels after repeated administration. Initial dose range-finding and toxicity studies help determine the maximum tolerated dose, identify observable signs of toxicity, and provide a rationale for setting dose levels in later definitive studies. The dose range tested in IND-enabling studies should be based on the dose range identified in efficacy studies, but, in order to establish safety margins, the dose range should be purposely engineered to exceed those levels and to exceed what would be done in the clinic.

Step 6: Meeting with the FDA

All of these steps ultimately lead to a pre-IND meeting and a subsequent IND meeting with the FDA. (See "The Basics of a Pre-IND Meeting" in the July/August 2014 issue of *Retina Today* for more information on pre-IND meetings.) The clinical trial protocol design will be based on the information gathered in the previous steps that describe the dose level, dose frequency, and potential safety concerns.

REPURPOSING

Repurposing is a phrase used to describe drugs that have been originally designed, and possibly used, for other indications, and have been reformulated for an alternative disease indication. There are many advantages to repurposing existing drugs for ophthalmic indications. An active pharmaceutical ingredient previously developed for a different indication already has known pharmacology, has been shown to be efficacious in relevant models or diseases outside the eye or for other ophthalmic diseases, and has existing toxicology information and known physiochemical parameters.

Put quite simply: Why reinvent the wheel? Repurposing gives a second life to compounds that may have been shelved due to systemic toxicity. Decreased systemic exposure following delivery to the back of the eye is a primary reason for considering the repurposing of a drug for a retinal indication. Many of the mechanisms targeted in treating systemic disease are the same pathologic mechanisms involved in ocular disease. This means that there are a number of drugs that have never been considered for the back of the eye.

CONCLUSION

Begin with the endgame in mind and make decisions accordingly. It is especially important during the preclinical stage. Although this article has described the preclinical process in a linear fashion, the process itself is continually subject to reverse loops. If development is stuck at a particular step, it may be necessary to backtrack in order to modify the compound and/or formulation and then proceed by repeating the process.

Thinking globally about the entire development process of a product and having clinical, regulatory, and quality control personnel involved early in the process are pivotal components to both preclinical and postmarketing success. ■

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