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Ocular translational science: A review of development steps and paths

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ABSTRACT

Developing successful drug delivery methods is challenging for any tissue, and the eye is no exception. Translating initial concepts into advanced technologies treating diseases in preclinical models and finally into functional and marketable products for humans can be particularly daunting. While referring to specific ophthalmic companies and products, this review considers key exchanges that lead to successful translation. By building on basic science discoveries in the academic setting, applied science can perform proof-of-concept work with simple, benchtop experiments. Eventually, simple models need to be translated to more robust ones where cells, tissues, and entire organisms are incorporated. Successful translation also includes performing due diligence of the intellectual property, understanding the market needs, undertaking clinical development, meeting regulatory requirements, and eventually scale up manufacturing. Different stages of the translation can occur in different environments, including moving from academia to industry, from one company to another, or between veterinary and human applications. The translation process may also rely on contract organizations to move through the complex landscape. While the path to a commercial, marketable product may not look the same each time, it is important to design a development plan with clear goals and milestones to keep on track.

1. Introduction

Translational research moves ideas and discoveries from basic bench science into real world situations that enhance human health and well-being. In medical product research and development, the aim is to "translate" findings from fundamental research into medical practice that can have meaningful health outcomes. Translational science involves coordinated interactions between cross sectional teams. Often, seamless transitions occur between team members with different areas of expertise and competencies. A multidisciplinary approach is required throughout the developmental process to enable effective translation of an idea or concept to an eventual product. Most importantly, translational research is not a passive process. It is a step-wise process that must remain plastic and fluid, shifting with changes in medical need, regulatory guidance, reimbursement patterns, economics and funding, and the standard of care competitive landscape. Ultimately, successful cross fertilization of ideas and development processes can translate into innovative products that will lead to improved health care value, health outcomes, and patient's quality of life.

There is clearly a global unmet need to treat and manage causes of blindness worldwide. Despite medical drug and device advances in glaucoma, improvements in cataract surgery, and innovative game changing intraocular injections of anti-VEGFs for wet macular degeneration and macular edema, these diseases and other ocular pathologies are still leading to blindness in millions worldwide [1]. In fact cataract, trachoma and glaucoma have accounted for more than 70% of global blindness [1]. Every year the number of blind increases by 2 million. The number is expected to double by the year 2020 [2]. To combat and eliminate avoidable blindness, thus reducing the global burden, the World Health Organization (WHO) has a WHO Global Initiative to Eliminate Avoidable Blindness, "VISION 2020: The Right to Sight", which aims to eliminate various causes of blindness as a public health problem by the year 2020. Cataract, onchocerciasis, and trachoma are the principal diseases for which world strategies have been developed, but glaucoma, diabetic retinopathy, uncorrected refractive errors, and childhood blindness are also recognized areas of unmet need leading to blindness [2].

The ARVO 2009 Summer Eye Research Conference (SERC 2009) on Ophthalmic Drug Delivery Systems is an example of the type of cross-pollination and multi-disciplinary actions occurring to move innovative ideas forward in ophthalmology. The conference was a co-sponsored meeting by the Association in Research in Vision and Ophthalmology (ARVO) and the National Institute of Health (NIH) [3]. The purpose was to expand and continue ongoing collaborative interchanges and synergistic endeavors from both academic ophthalmology and the ophthalmic pharmaceutical industry, including bench side researchers and physicians. Discussions centered around recent advances in drug delivery systems that could improve drug delivery to the back of the eye, and how these devices and technologies might be successfully used in

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commercial products. The meeting focused on ways to enable the development and translation of improved methods to deliver drugs to the eye, highlighting the unmet ophthalmic medical need and the need for collaborative interactions across various critically involved parties—industry, government, and academia. The ophthalmology community has taken this cross-fertilization and innovation one step further with yearly Ophthalmology Innovative Summit meetings. These summit events have helped facilitate meaningful interactions and business partnerships between physicians, entrepreneurs, and investors, thus enabling the funding and strategic partnerships needed to develop and translate innovation in ophthalmology.

The translation process of moving ideas and results from academic bench into industry, and into clinical trials, that will ultimately lead to an ophthalmic product within the commercial space, is a critical and complex process. In this review, we discuss aspects of this translation process, including preclinical models that are used to move a concept toward clinical trials, moving from basic science into the corporate environment, translation between the veterinary and human medicine space, and commercialization considerations necessary to complete the translational process to producing real-world products.

2. Translation through preclinical models toward clinical trials

The concept for a product often starts with applying the knowledge gained from basic science research to a specific medical need or problem. Prototypes of this product concept must then be generated and tested in preclinical studies to demonstrate both safety and efficacy before moving into humans. A sponsor may want to have an idea of the efficacy before moving into clinical trial, yet the FDA sets human safety as the priority. Thus, the ultimate goal of preclinical trials from the FDA's perspective is to provide animal pharmacology and toxicology testing to support the decision that it is safe enough to move into humans. The FDA will not list specific animal models as being required. A sponsor submitting a drug for approval must consider laws, regulations, policies and procedures. Resources for these items would be: The Federal Food, Drug, and Cosmetic Act; Code of Federal Regulations; Manual of Policies and Procedures; and FDA Guidance Documents. For example, a sponsor may voluntarily qualify an animal model (a specific combination of an animal species, challenge agent, and route of exposure that produces a disease or condition and corresponds to a human disease or condition). This can provide some generalization for use of the model in the future and could potentially speed up the drug development and review process. However, use of a qualified animal model does not guarantee that it will be deemed suitable for the new drug.

The preparation work before entry into clinical trials can include a spectrum of simple to advanced models for testing the product. Preliminary bench-top models are often used to demonstrate an initial proof-of-concept. Introducing biology with in vitro models can be effective in testing the safety and efficacy at the cellular level. On the other hand, harvesting biology in ex vivo models are often useful for testing a product at the tissue or organ level. In silico models can be beneficial in improving other models. Ultimately, both safety and efficacy need to be tested in vivo, and a complex living animal presents a significant challenge with realistic pathophysiology, complete anatomy, and intact drug delivery barriers. Moving from simple to more advanced models has tradeoffs in control and repeatability versus more realistic and predictive results, as well as increased costs as the model increases in complexity. Specific models cannot be recommended for regulatory requirements as suitability is determined by the FDA on a case-by-case basis. The purpose of this section is merely to review models that have been used for ophthalmic applications (with a translational perspective).

2.1. Benchwork models

Preliminary benchwork models can be useful in obtaining answers to specific questions or for proof-of-concept work. Necessary preliminary work could be simple static release studies in test tubes for a drug delivery device. While such conditions may not be indicative of volumes and turnover rates for tears in human eyes for example, it allows for quick testing of different drug delivery designs to see how each iteration compares to another. There may be merit in simulating the tear volumes and turnover rates as this may result in more sustained release rates [4]. It has been seen in situ with humans that tear flow rate limits the diffusion of fluorescein out of a collagen shield [5]. An article associated with U.S. Pharmacopeia provides recommendations for dissolution testing with simulated tears, and additional recipes for gastric and intestinal fluids may be helpful if there is a chance for drainage of product through the nasolacrimal duct [6]. More sophistication is possible by modeling the anterior and posterior sections of the eye with simulated fluids to more thoroughly study the release and distribution potential [7]. These types of models are useful for providing an initial assessment of the safety and efficacy of the product regarding localized drug concentrations.

2.2. In vitro models

For additional efficacy testing, cell culture models are beneficial for modeling transport across cellular barriers as well as demonstrating drug activity following transport with a drug delivery device [8,9]. However, limited availability of human ocular cell lines, long culture times, and phenotypical changes are challenges to overcome in this model [8]. Still, in vitro cell culture models seek to replace animal models with controlled parameters and reproducible results [10]. There is also the advantage of being able to test the safety (such as genotoxicity) of drugs and materials before risking harm to live animals or humans [11]. The hen's egg test on the chorioallantoic membrane (HET-CAM) model provides a highly-vascularized test bed that can be used for ocular irritation and neovascularization studies [12,13]. For specific applications, tissue engineered constructs are now available and can produce more complex in vitro models, such as a corneal tissue model, with either normal or diseased tissue, or a trabecular meshwork model [14,15].

2.3. Ex vivo models

When cell culture and tissue engineering models are not sufficient, ex vivo models offer a compromise to the need for complex tissue structures and the ethical concerns of experimenting on live animals, as human or animal tissues can be obtained as excess from other research studies or other alternate sources (organ donations, slaughter houses, etc.). A simple ex vivo technique may involve harvesting just the vitreous humor to be used for stability and diffusion testing [16]. Alternatively, tissues may be harvested to test drug transport phenomena in various ocular barriers. Ex vivo tissue can be placed in a Franz cell, Ussing chamber, or other custom built apparatus to test the passive and active transport of drugs across the cornea or sclera [17–19]. Models of ex vivo transscleral delivery can provide effective diffusivity coefficients that can be compared between animal species and humans [17,20].

2.4. In silico models

Complex transport phenomenon can be modeled mathematically with the aid of computers. These in silico models can improve the efficiency and accuracy of other models or can be used to quickly screen product design iterations. In silico models are flexible and able to model drug delivery to the anterior or posterior portion of the eye—even down to the cellular level [21–23]. There are options on how detailed to make the compartment models: simplified with only a few compartments, include all periocular spaces, or whether to consider states of “still in formulation” vs “dissolved and available for transport” [22]. Beyond pharmacokinetics, biomechanical modeling can aid preclinical development of ophthalmic devices and drug delivery strategies

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