Defining the Problem in Ophthalmic Drug Development and Clinical Translation

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Abstract

Albert Einstein once noted: “If I had only one hour to save the world, I would spend fifty-five minutes defining the problem, and only five minutes finding the solution”. In medicine development, the process of defining that question is about identifying the “entry point or break point or gap” for next steps. The success of drug discovery and development is built upon decades of deep scientific research and clinical evidences, through back-and-forth development & validation of the integrative sciences, and takes cross-functional team efforts. This review is to address some of the key issues in clinical trials and translational gaps, what we can do to improve, and which areas are the technology limitations or disease inherited problems that we do not yet have the leverage to navigate. Specifically, the author emphasizes the importance of drug molecular mechanism match precision in target disease indication, which is the scientific basis of product medical strategy for improving clinical translational efficiency in early and late stage drug development. Retina and glaucoma therapeutic targets are the key highlights. Closing remarks elevate the content to the strategic leadership and talent skill set that helps to define the future of medicine development path.

Keywords: Clinical Translation; Safety and Efficacy; Gaps; Retina; Glaucoma; Leadership Talent

Introduction

No human being is perfect, even perfect eyesight with 20/20 vision has a blind spot. The 21st century has ushered us into an unprecedented new era of science and technology revolution. Overwhelming vast information explosion and digital data penetration are terrifying, and lifelong learning is not a choice but a must. Yet this is far from enough. A mindset of being open to welcome different opinions and critiques from all professional ranks will be a key to better adapt into this new modern world. With increased lifespan and quality of life, medicine is becoming the central domain in life sciences. Traditional drug development model must change in order to take the advantage of such volatile fast-moving scientific revolution. Each year Pharma biotech and private ventures invest multi-billion dollar in drug discovery and product development; US government and NIH spend billion dollars in academic institutes on educating talents and producing basic sciences. Sadly, many researchers are endeavoring in the dark box whilst not seeing the forest for the tree (tunnel vision); tons of scientific discoveries are scattering in campus. Industry patent cliffs are threatening R&D pipeline; lengthy expensive clinical trials fail at >90% rates [1], which is most shocking. Can we change the course and do it differently?

The Root Cause Analysis of Translational Failure

The answer is “Yes”, but first we must realize this is a translational problem. To solve such problem we need to start with people and change the conventional mindset first, and then we can focus on technical aspect of the big “why”. I have conducted extensive clinical research and helped senior leaders trouble-shooting on a broad array of new treatments or assets in ophthalmic therapeutic development, which enables me to gain a global spectrum and deep scientific insight into the root causes of these failure or success stories. More importantly, I have identified two key translational gaps [2]: The first gap is from pivotal preclinical to early stage clinical development, which
counts for ~60% failure, due to the following reasons: 1) disease root causes are not clear or too complex such as age-related macular degeneration (AMD) and dry eye diseases; 2) preclinical animal model is not proficient, and only reflects a simple or limited aspect of the disease molecular pathological processes [3]; 3) target mechanism of actions (MoAs) mismatch with patient population (disease staging); 4) lack of surrogate biomarker/endpoint to further a sound go/no-go decision; 5) ocular drug delivery presents an emerging challenge in pharmacotherapy for posterior segment diseases, of which retina and glaucoma are the two major therapeutic areas representing the most lucrative pharmaceutical market in eye care space [4]. The second gap is from early stage translation (Phase 1/2) to mid-late stage clinical development (Phase 3) towards regulatory approval, which counts for 30% failure at either safety or efficacy. In this transition, that MoAs mismatch (partly or completely) with the exact clinical phenotype in patients becomes a predominant issue, especially in the diseases involved with multiple pathophysiological processes such as AMD, diabetic retinopathy (DR) and glaucomatous neuropathy. However this can be improved by introducing “product medical strategy (PMS)” into clinical development frame work (e.g. clinical synopsis). On safety arena, most eye diseases are chronic in nature thus require long-term and sustained treatment via multiple or frequent dosing with more than one therapeutic alterations, which may increase the risks of drug-drug interaction and accumulative side effects that is imbalance with the decreased threshold of safety tolerance in aging population. Nevertheless, treating eye disease is about local delivery that is so far the most effective route. Compared to systemic drug administration, ocular drug delivery has an advantage in reducing drug systemic exposure (by 95%) [4], hence adverse events such as cardiovascular renal failure are very low in eye care clinics. In order to navigate above mentioned technological limitations or disease inherited problems, human factors play an important role. One must have the ability to “see” both sides of the bridge (bench and bedside), and develop high-level integrative skill and synthetic thinking. Unfortunately, such integrative talents are far short in biotech and Pharma industry. This perhaps is one of the key human factors attributing to the 90% failure during early and late stage of clinical translation.

Insight of Early Stage Clinical Translation

For small molecules or antibody drugs, MoA and drug potency define the safety and efficacy profiles in given patient population (subset). Specifically, drug potency and binding affinity (EC50/IC50) governs a drug pharmacological trend such as dose/dose response curve and on-target/off target profile. In early stage clinical development, it’s vital to capture early clinical signs or data signals pertinent to drug molecular trait, otherwise, the clinical strategy could easily deviate from the mainstream development track and miss out the right patient pool, which ultimately leads to efficacy failure. In the light of AMD therapeutic development, the vision loss is caused by multiple molecular pathological entities that interplay in a dynamic fashion over many years, one single drug may be only effective to a very limited subset patient at a given disease stage. That’s the reason why we will need to develop different therapeutic targets and employ combination therapies (mono, combo, triple) to address different pathological root causes (like treating cancer). How to play out these therapeutic algorithms (when, what and how) while considering on dosing strategy is at a high stake between success and failure.

Compare to pharmacotherapy, gene and stem cell replacement share one common advantage in translation that is MoA match precision with patient. The key focus should be at developing an individualized treatment, specifically on delivery parameter and dosing strategy based upon clinical phenotypic and disease pathological entity. The selection of promoter and vector is another key technical challenge that needs to be born in mind whilst considering on delivery route. Nevertheless, eye or retina is an excellent translational tissue organ for gene/cell therapy due to its immune-privilege site, accessibility, and visibility (thanks to advanced ocular imaging technique). Decades of the efforts being made on retinal gene therapy have allowed us to establish enough confidence about virus related clinical safety surveillance based on studies in various animal models and human subjects. In recent 8-10 years, there are emerging early stage clinical trials of retinal gene replacement targeting on rare inherited degenerative conditions such as retinitis pigmentosa (RP), Stargadts, retinoschisis, choroideremia (Ph1/2). The most advanced program perhaps is RPE65 (retina pigment epithelium) gene replacement therapy for LCA (Laber congenital amaurosis) at Phase 3 (UPenn/UCL). However, recent evidences have raised a new question about long-term clinical efficacy in LCA trial patients, because the sustainability of genetic transfer in a diseased setting might not be a lifelong as we had thought before. Also, one must realize that the same genetic mutant could be associated with broad clinical phenotypes in the range of disease onset (early vs late), severity and nature course as well as tissue/cell involvement, which can be varied

from patient to patient. Therefore, understanding genetic related clinical phenotype and host tissue/cell interface biology is extremely important for designing individualized dosing strategy and delivery parameters.

Stem cell therapy is a younger cousin of gene therapy in retina therapeutics. Most clinical trials are at its infancy in the sense that researchers are still exploring different cell types as donor source. One of the most promising cell targets is RPE replacement for advanced macular degeneration where RPE atrophy or defect is a predominant pathology. Embryonic stem cell derived or iPSC (pluripotent stem cell derived) RPE sheet or cell suspension transplant represents a key advancement in this area (e.g. Astellas/Ocata and Riken Center in Japan). On the other hand, photoreceptor replacement (e.g. ReNeuron) is one of the most challenging tasks because it involves with the reconstruction of light sensitive neural circuit. Unlike drug MoA target, we have little understanding about donor-host cell interact in the ongoing degenerative pathological environment, and how these newly formed graft cells remodel or alter disease intrinsic molecular pathological processes and microenvironment milieu is an area that requires deep and sophisticated translational expertise. There is a big "gulf", not a gap to bridge, which may take decades of work in order to get to the point of what pharmacotherapy has achieved today. Like genetic based protein drug delivery, stem cell therapy has gone beyond the replacement arena. Many researchers are garnering the biological merits of various tissue lineage stem cells or progenitors for neural protection or immunomodulation. For example, Stem Cell Inc. is conducting Ph2 clinical trials of brain-derived neural progenitor cell transplant in the hopes of rescuing photoreceptor loss in patients with advanced AMD or RP.

Late Stage Clinical Translation & Product Medical Strategy (PMS)

PMS is to position a new drug into specific clinical indication (could be one or several niche indications) whilst considering on global competitive market and current standard care. A new investigational drug can be positioned as the first line, or second line or add-on in combination therapy for the designated clinical indication or disease phenotype. In conventional drug development model, PMS has been widely used for post marketing commercial strategy and product penetration; however the concept has evolved rapidly in meeting the new challenge of translational medicine. Designing a comprehensive PMS is becoming a new standard and a “must” piece prior to any stage of clinical trials, especially pivotal Phase 3 studies that defines the territory of regulatory label and helps establishing solid evidences to show e.g. what type of patient may benefit from what merits of the new investigational drug. Without PMS in place, Phase 3 trials could fail or lead to suboptimal outcomes due to the missing of primary clinical endpoints or additional niche indications. In large Pharma, many business units have introduced PMS to assess new opportunities and market potentials or design product target profile at very early stage of drug development. As such, the new demand for such strategic talents has increased significantly, especially in late stage medical affairs. McKinsey 2020 Vision layout a promising blueprint of medical affairs function in pharmaceutical drug development [5]. How does big data and patient centric real world experience shape up R & D taskforce? From leadership talent perspective, one must have the following three integrative skill sets: 1) strategic vision and think like global marketing leader, 2) clinical experience and know-how tactics; 3) have deep scientific expertise, act like R&D leader. This is a hard ball to play in executing global medical affairs strategy.

Pharmacotherapies for glaucoma IOP (intraocular pressure) control and retina angiogenesis are the two leading territories, of which medical affairs have well-established network infrastructure and extensive experiences. In particular, glaucoma IOP lowering drug market has a long-standing history, which provides the richest experience and data base gathering from more than 10 products being marketed worldwide (e.g. beta blockers, prostaglandin analogues, alphagan, CAI and combination products). As such, we may take a great advantage of the well-established regulatory path, and yet IOP reduction as a single endpoint measure is far from proficient in this emerging competitive glaucoma market. The treatment paradigm is shifting towards on achieving long-term IOP stability (avoiding spike) and dosing advantage (sustained drug delivery) as well as visual functional stability, among which reducing retinal ganglion cell (RGC) loss is the ultimate goal in glaucoma patient care. There are dozens of IOP independent risk factors attributing to the RGC death (apoptosis or necrosis) in glaucoma [2]. So far IOP is the only risk factor that can be managed clinically. For decades, neural protection has been the Holy Grail in glaucoma and retina research. Notably, the lengthy Memantine neural protection trials in glaucoma failed...
a decade ago (Allergan), partly due to insufficient delivery and the complexity of disease molecular pathological processes. Recently Allergan repositioned the glaucoma IOP lowering drug, brimonidine (alpha2-adrenergic receptor agonist) as a neural protection candidate for glaucomatous neuropathy, dry AMD, RP and retinal detachment through Ph1/2 clinical trials, which seemed not yielding favorable results, partly due to its MoA mismatch with the disease molecular pathological condition in the retina, e.g. choroid ischemia is an important causative factor in dry AMD (Alan Bird, MD, UCL), whereas Brimonidine has vascular constrictive effects. Looking forward, glaucomatous neural protection trial remains one of the most challenging doubting tasks in decades to come. One of the cost-effective tactics is to take steps. For compounds that have dual mechanism of actions on IOP reduction and RGC protective potentials (e.g. Trabodenoson by Inotek Pharma), we could start gathering early clinical evidences (secondary endpoint) pertinent to the RGC survival during the late stage large clinical studies focusing on IOP parameters (primary endpoint). These neuroprotective signals or clinical evidences from glaucoma patients can be extremely valuable in offering a different perspective of the drug molecular traits, which can’t be learned from preclinical animal models. Encouragingly, ocular imaging advancement has shed a new light on our better understanding of structure-functional relation in glaucoma whilst looking at the retinal nerve fiber layer and visual function loss-the tipping point (Joe Schuman, MD, NYU) [6]. This is a very important technical milestone for monitoring the disease progress in glaucoma, also offers sensitive and quantifiable clinical biomarkers for efficacy evaluation (on RGC neural protection). In parallel, it’s very important to work closely with regulatory agencies to establish the new standards and guidelines for accelerating the process of regulatory approval and international conference harmonization (ICH) [7].

Anti-VEGF therapy (Lucentis, Avastin and Eylea) has revolutionized the way of how retina specialists treat patient since 2005 [8-10]. Clearly the new generation therapeutic target has to focus on addressing the disease root causes of wAMD and early stage dry AMD (Prof. John Marshall, UCL). Unlike the IOP readout in glaucoma, neurovascular lesion within the retina (wAMD or RP) is much more complicated, for which the existing clinical endpoints such as visual acuity and central retina thickness are not sufficient in capturing the drug unique molecular trait corresponding to its clinical implications. Hence the new standard of wAMD clinical trial will have to consider “additional” quantitative clinical parameters such as dosing advantage, treatment burden, sustained long-term visual benefits (e.g. >5 years), and the phenotype switch to atrophic lesion (ischemia). On the other hand, we have noted that the emerging post-marketing real world experience of anti-VEGF therapy is very different from the pivotal Phase 3 clinical results, for which understanding the treatment caveats and disease problems will be extremely valuable to advancing new drug discovery and target identification for AMD. This is a “reverse” step in translational medicine (from bedside to bench). Rescula (unoprostone) is another extreme example of how post marketing experience is reshaping the landscape of Rescula clinical profile that was not shown in the pivotal Phase 3 studies, further advancing the new discovery of unoprostone as a B-K channel activator (not prostaglandin analogue) [11]. Clinical biomarkers continue evolving as an important part for translational medicine taskforce, e.g. the success of human genome project along with the readiness of clinical genetic test (e.g. complement factors) may help to better define target patient population in both dry and wet AMD clinical trials. Advanced retina imaging techniques such as wide-field fluorescein angiography, confocal scanning laser ophthalmoscopy, high resolution spectrum domain OCT (optic coherence tomography), OCT angiography, and micro perimetry may offer better quantitative assessments for therapeutic development targeting on dry AMD, with which we might be able to reduce the length of dry AMD clinical trials from 2-3 years to a few months (9-12 months).

**Two Key Considerations: Efficacy & Safety**

In ophthalmology, there are two categories of therapeutic targets. One is targeting on 20/20 vision or driving vision (e.g. anti-VEGF therapy on wet AMD), the other is to help those who are legally blind due to irreversible end-stage retinal degeneration e.g. artificial retina prosthesis for end stage RP (11). Understanding patient expectation and disease severity will be important for designing differential clinical strategies whilst considering on dosing, safety and efficacy endpoints. Thanks to the local delivery, most ophthalmic drug developments fail at efficacy rather than safety. Like systemic drug development for cancer or neuroscience or cardiovascular disease, clinical development is about “validation” of efficacy and safety in the targeted patient population. The strategic goal must focus on patient benefits against the regulatory guidance. In general, efficacy is looking at “on-target” (site of action) biological effects and its
related pharmacological profile of the tested drug. Different diseases or clinical phenotypes that share the same molecular pathological pathways may benefit from the same drug or treatment, which is the scientific basis for "repurposing" or indication mapping, or PMS. Within the therapeutic dose window, drug pharmacological profile and biological activities should be favorable and within the physiological tolerance. On the other hand, clinical safety covers much broader spectrum of pharmacological responses occurring outside of the target tissue, called "off-target" side effects or adverse events (often harmful) derived from parent compound and its metabolites, and may occur across multiple tissues and organs in the body and over a period time (cumulative). One of the important parameters to define whether or not a new compound or antibody is "druggable" is that the on-target signals (efficacy) must surpass the off-target signals (or adverse effects). If the compound is druggable, fine-tuning therapeutic dose will be a key to help define the margin between efficacy and safety in preclinical models and the target patient population. Separately, ocular tolerance and systemic safety are the important aspects for patient compliance in the elderly population, who may suffer multiple systemic and/or ocular comorbidities.

In modern medicine development, we often hear about “one size does not fit all”. Individualized therapy is in particularly important for gene/cell therapy; blockbuster drug making often is built upon multiple small niche indications. In the era of big data, it’s important to have clear vision and focus, otherwise, one could easily get lost in the drug validation process. Like building “Legos”, we always need to have a strategic “map”, which is equivalent to PMS in drug development. At an organizational level, leadership is essential to ensure a smooth cohesive clinical operation and strategic alignment. Portfolio optimization has to take the risk-benefit assessment into consideration, for which product efficacy and safety are the core measures.

Closing Remarks

In literature, in order to translate Shakespeare into a foreign language, not only do we need to be bilingually proficient, but also need to fully appreciate its culture context and histological background. In a similar vein, medicine translation needs integrative talents with technical know-how and business acumen as well as creative thinking. We have to think outside the box but must work within the box, and focus on the two fundamental questions: “does it work, is it safe”? In different from academic research, pharmaceutical clinical validation requires high-level “integrative” problem solving skills. Yet, defining the key problem is far more important than finding the solution itself. While speaking of integration, we should acknowledge that everything in the universe is connected. In Steve Jobs’ word, “creativity is about connecting things, you must have enough knowledge and experience so that you may have enough dots to connect and form non-linear solutions to solve the problem”.

The 21st century is a very exciting era in modern medicine. Pharmaceutical globalization and market competitiveness are urging each one of us to adapt for unpredictability whilst embracing the tiding wave of technology explosion. Global strategic leadership is becoming ever more important for cultivating collaborative culture so that individuals or team can leverage internal and external resource and expertise in a cross-functional and cross-geographic fashion. Integrity, vision, intelligence and passion are the key leadership essentials. In business it’s the people that make the difference. Undoubtedly, biopharmaceutical business revolution is exerting positive impact to academic research and educational trainings by emphasizing on “creativity and application”, which collectively may transform the future landscape of both public and private R&D and education systems.

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Bibliography


