

New Frontiers of Retinal Therapeutic Innovation & Strategic Insights

Tina Guanting Qiu* (review by Alan M Laties, MD)¹

¹ Department of Ophthalmology, University of Pennsylvania, USA

***Corresponding Author:** Tina Guanting Qiu, MD PhD, Biopharma Physician & Executive Consultant, 3212 Crane Brook Way, Peabody MA 01960 USA.

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Abstract

Modern medicine development is alike unlocking mystery of black box. The journey of 10- year drug development is about establishing a drug molecular biological trait along with its pharmacological behaviors in animal disease models and various human conditions. Product medical strategy has become ever more important in bridging gaps for translational efficiency. This review focuses on the paradigm shift of therapeutic intervention for retinal diseases. Topics include: 1) Emerging ocular drug delivery innovation from polymer-based sustained-release drug delivery to genetic engineering protein biofactory (superachoroidal and subretinal routes begin to merge). 2) New themes of tissue rejuvenation and parainflammation in retina and glaucoma disease management. 3) New highs in disease alteration by emerging therapies - the switch from “wet to dry” vascular AMD (age-related macular degeneration) is a great example of such in the new era of anti-VEGF therapy. 4) Bio-therapeutic innovation at a glance. 5) Understand disease staging and phenotype stratification is “A Must” in developing personalized treatment algorithm. New evidences suggest that AMD represents a group of heterogeneous clinical pathological entity that includes RPE aging, photoreceptor loss, Bruch’s membrane thickening, and choroid ischemia, among which one or more can be the primary trigger and predominant clinical phenotype. New appreciation of glaucoma as a neural degenerative disease involving pressure-dependent and pressure-independent risk factors may lead to breakthrough of neural protection drug development in the 21st century. In summary, reduce photoreceptor and retinal ganglion cell loss is the ultimate goal of therapeutic intervention for a large spectrum of significant neurovascular diseases in the retina. (254 words).

Keywords: *Glaucoma; Parainflammation; Photoreceptor; Retina; Eye; Rejuvenation*

Introduction

In the retina, there are two biggest problems spanning at two extreme ends. One end is about cell proliferation such as choroid neo-vascularization (CNV), proliferative vitreoretinopathy (PVR), proliferative diabetic retinopathy (PDR), epiretinal or subretinal fibrosis and scar formation, as well as inflammatory cell proliferation. The other end is abnormal cell loss due to apoptotic and necrotic cell death in various genetic or acquired pathological conditions, such as age-related macular degeneration (AMD), glaucomatous neural degeneration, retinitis pigmentosa (RP) and Stargardt’s macular degeneration (SMD), for which regenerative medicine comes into a play. In the past two decades, scientific advances have allowed us to gain in-depth understanding of molecular pathophysiological mechanisms involved retinal diseases, which are changing the way of how we treat patient and how we project future medicine.

This review covers both clinical development and cutting edge technologies with new themes on basement membrane rejuvenation and parainflammation along with some of the most exciting happenings in retina and glaucoma disease management for the back of the eye. In the light of retina therapeutic area: 1) The appreciation of dry AMD clinical sub-phenotypes is paving the way of precision medicine development for early stage AMD clinical trials (e.g. patient enrollment). 2) Long-term anti-VEGF therapy is altering vascular AMD nature course with a switch from wet to dry clinical phenotype. 3) New minimally invasive sustained-release ocular drug delivery along with

novel genetic and RNA based protein bio-factories are ophthalmic innovation frontiers. In glaucoma, the disease management has shifted its paradigm from simple IOP reduction towards long-term IOP stability and neural protection through modulating non-IOP dependent risk factors. On surgical front, micro-invasive glaucoma surgery (MIGS) plus Phaco cataract removal are offering new alternatives for early stage glaucoma treatment algorithm. Additionally, as we know macula is in charge of the most precious vision in our life. A rising wave of low dose steroid sustained delivery for refractory diabetic macula edema (DME) is deepening our understanding about the disease pathological entities, which are not a simple VEGF caused vascular disease but involve significant chronic parainflammation. Finally the game ends with severe retinal ganglion cell (RGC) and photoreceptor cell loss. So far, the only solution is replacement via either artificial retinal prosthesis (e.g. bionic eye) or stem cell regenerative medicine.

1. New Advances in Age-related Macular Degeneration (AMD)

1.1: AMD Clinical Sub-phenotypes and Root Causes

AMD is the leading cause of irreversible visual devastating disease in western country in age over 65-year old. In textbook, drusen is the hallmark of dry AMD. Well, what if patient does not have drusen, does he/she have AMD? Recent studies have demonstrated that there are 4 predominant subclinical phenotypes associated with early stage AMD, among which one or two more could be the predominant driven forces for disease pathological progress towards advanced stage [1,2]. These four pathological clinical sub-phenotypes are 1) Retina pigment epithelium (RPE) atrophy due to aging. 2) Photoreceptor (cone) loss can be a primary trigger. 3) Bruch's membrane aging is the rate limit pathological process for AMD (Prof. John Marshall). 4) Choroid ischemia (capillary patchy loss) is a hidden devil that is beginning to receive attention (Prof. Alan Bird). Finally parainflammation and complement pathway are the new themes for therapeutic targets on dry AMD.

With the huge success of anti-VEGF therapy for wet AMD, treatment paradigm has shifted toward pathway-based therapeutic strategy to addressing various root causes associated with early stage dry AMD. Figure 1 depicts a road map of these baby-boomer early phase clinical trials, among which anti-complement factor D (lampalizumab) via intravitreal injection perhaps is the front-runner at Phase 3 showing a promise in preventing geographic atrophy (GA) and vision deterioration in patients with dry AMD [3]. Retina rejuvenation therapy (2RT) is a rising star being developed by Ellex for the treatment of drusen in dry AMD, which has showed encouraging clinical results on the clearance of patchy or dotted drusen in phase 2 clinical trials [4].

1.2: Effects of Long-term Anti-VEGF Therapies on Wet AMD

Since the first pathway-based anti-VEGF therapy Lucentis was brought to market back to 2002, emerging anti-VEGF drugs including Eylea and Avastin (off label) have revolutionized pharmacotherapy for vascular retina diseases including subretinal choroidal neovascularization (CNV). Yet there are two rising problems associated with long-term anti-VEGF treatment. According to Seven-Up study report in 2013, after 3 years Lucentis treatment, one-third of the treated patients may gradually lose their vision due to subretinal fibrosis or scar formation, or increased geographic atrophy [5]. These late stage subretinal CNV lesions often contain complex cellular components such as macrophage and microglia infiltrations, Muller glia cell remodeling, and fibroblast proliferation. As of result, the CNV pathological entity may evolve from early stage VEGF-driven microcapillary lesion towards late stage arteriolarized new vascular lesion. Thus, they do not respond well to anti-VEGF treatment. Ophthotech (NY) is pioneering 3rd generation wet AMD therapeutic strategy with a clinical phase 3 target, anti-platelet-derived growth factor (anti-PDGF) called Fovista in combination with Lucentis to address this rising pandemic fibrotic problem, which has showed significant efficacy and favorable safety [6]. Another phenomenon is the switch from wet to dry clinical phenotype. According to the CATT study group report in 2014, anti-VEGF treatment may drive the "wet" CNV lesion converging into advanced geographic atrophy (GA) with increased and well-demarcated RPE atrophy, which is similar to de novo dry AMD [7]. Ocata Therapeutic (MA) is pioneering the first human embryonic stem cell derived RPE transplant to address such significant RPE loss in various advanced macular degenerative diseases, including dry AMD, SMD, and myopic macular degeneration. They are at phase 2b clinical development with encouraging future prospect [8].

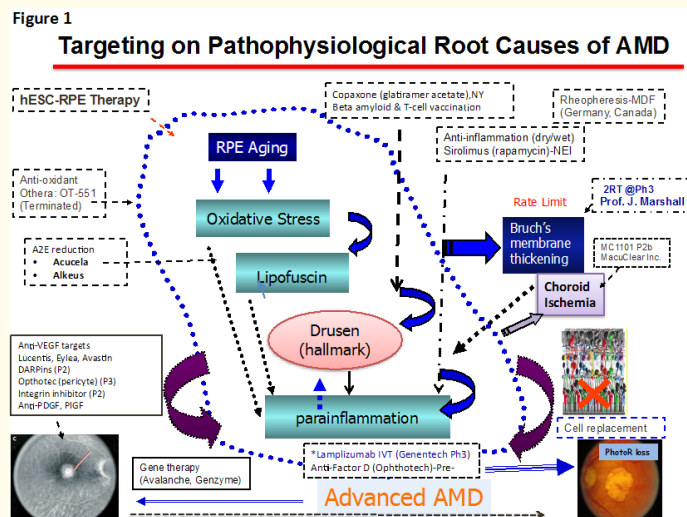


Figure 1: AMD Pathophysiological Pathway & Therapeutic Targets. Presented at MassBio Signature Event on October 17, 2012, Cambridge, USA.

2. New Horizons on Glaucoma Disease Management

2.1: IOP dependent and non-IOP dependent risk factors

“In glaucoma clinic, some patients, no matter how you treat them, they still go blind” cited from Dr. Kuldev Singh, President of America Glaucoma Society-2012. This entails a truth that IOP independent factors play important roles in glaucomatous neural degeneration. Therefore, current standard of care by reducing IOP alone suffers a great limitation. Normal tension glaucoma (NTG) is a classic example that multiple vascular and intricate inflammatory components (ET-1, TNF α , NF-Kappa) other than elevated intraocular pressure alone are responsible for the sneaky vision loss in this subset disease category [9]. The Figure 2 highlights different cellular compartments (e.g. mitochondria, microglia), key pathological signaling pathways (ischemia-reperfusion damage, NF-kappa B based parainflammatory pathways) and multiple causative factors (glutamate, calcium influx, TNF-a, beta amyloid, beta crystalline), which are contributing to RGC death in glaucoma disease pathological progress. Among these causative factors, neurovascular imbalance and parainflammation have received great interests in both academic and industry, which indicates a strategic importance for drug discovery and development for glaucoma patient care.

2.2: A New Prospect of Neural Protection for Glaucoma/Retina

Neural protection has been century dogma. The 20th century has been an era of neurotrophin (NT) based interventional approach via tyrosine kinase signals for both central nervous system (CNS) and retina degenerative disorders. A cluster of neurotrophic growth factors, such as NGF (neural growth factor), BDNF (brain-derived neurotrophic factors), CNTF (ciliary neurotrophic factor), NT 3, and NT 4/5 have been exhaustively studied and tested in various preclinical disease models and early stage clinical trials in patients with RP and AMD. So far, there has not been any success yet. Looking forward in the 21st century, we believe that preventing neuronal cell death (neural protection) has to be proactive either through regenerative approach or directly addressing the fundamental root causes underlying cell apoptosis or necrosis. Currently there are three new class small molecules being evaluated for their potentials to rescue retinal ganglion cell and/or photoreceptor death in glaucoma and various retinal conditions. Trabodenoson (Inotek Pharma) is a new class of adenosine mimetic highly selective to A1 receptor (A1R), which is being developed for glaucoma IOP management with additional evidence of rescuing RGC from ischemia-reperfusion damage in preclinical rat model. Unoprostone isopropyl (rescula, 0.12% eye drops) is a newly discovered B-K channel activator with great advantage of pre-existing market experience since 1994 [10]. Currently the same formulation is being tested in Phase 3 clinical trials for RP in Japan (R-Tech Ueno) [11]. Based on author’s recent investigation and

understanding about B-K channel activation, unoprostone may have broad pharmacological and therapeutic implications in modulating neurovascular imbalance, choroid ischemia and parainflammation in certain subset clinical phenotypes. Similar to rescula, Brimonidine (0.2% or 0.25%) is also a very old ocular hypotensive drug, which is being repositioned through sustained release intravitreal implant for its neural protective potentials in various retinal abnormalities (Allergan) [12]. Of important note, Brimonidine is vascular constrictive, which may contradict with disease pathological process involved with choroid ischemia and neurovascular problems, such as AMD and NTG. Perhaps this might explain why recent Phase 2 clinical trials on dry AMD, RP, glaucomatous neuropathy and macular-off retinal detachment have not achieved satisfaction yet [13].

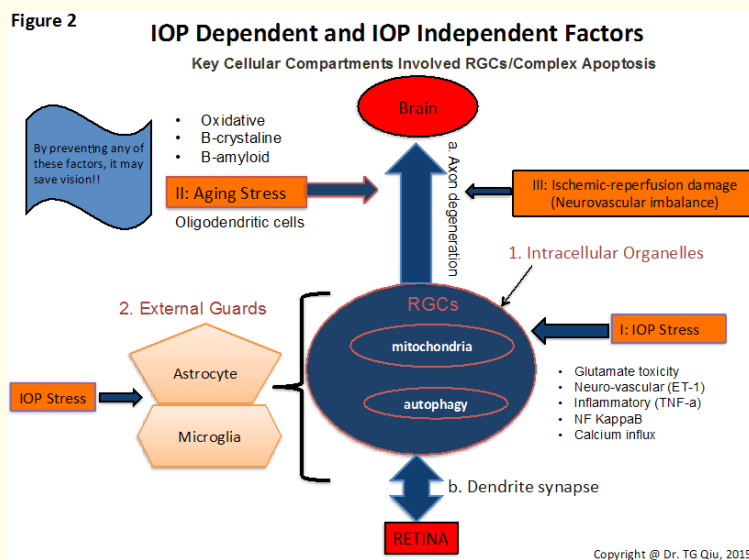


Figure 2: Glaucomatous Neural Degeneration & Retinal Ganglion Cell Death. Presented at Eye-2015 International Conference on July 13-15, 2015, Baltimore, USA.

3. An Eye on Basement Membrane Rejuvenation for Glaucoma and Retina

The concept of regenerative medicine has gone beyond tissue organ transplant. For example, the “tales” of basement membrane rejuvenation are being flourished by the early clinical success of nanosecond pulse laser triggered extracellular matrix (ECM) rejuvenation in Bruch’s membrane and pharmacological agent induced trabecular meshwork (TM) rejuvenation. Both methods involve of cascade ECM remodeling process through on-site activations of matrix metalloproteinase (MMP) enzymatic pathway. Professor John Marshall’s early research suggested that MMP treatment could help turn 60y old Bruch’s membrane back to 40y old with increased hydraulic conductivity and flexibility [1,14]. Based on this notion, the first 2RT clinical trial on DME patients was conducted in 2008 at Kings College London, which has showed significant VA (visual acuity) improvement at 3 and 6 months [15]. Additional 2RT laser clinical studies on dry AMD also have demonstrated measurable clinical benefits evidenced by drusen resolution and GA stability at 6 and 12 months. Unlike conventional laser photocoagulation, 2RT targets on single RPE level, which exerts very minimal damage towards adjacent photoreceptor neurons, therefore 2RT can be repeated in due course over time. With aging population, tissue rejuvenation has strategic importance in stem cell therapy and regenerative medicine. For example, recent human embryonic stem (ES) cell derived RPE therapy being developed at Ocata Therapeutics offers a healthy cellular source for RPE replacement, perhaps more importantly, these healthy “young” RPE cells might contribute to Bruch’s membrane remodeling and rejuvenation through paracrine secretion of various cytokines and protein enzymes, among which MMP family would be an important one.

In glaucoma pharmacology research, adenosine A1 agonist, cyclohexyladenosine (CHA) has been showed to trigger sequential MMP activations via A1 receptor (A1R) in trabecular meshwork cells [16]. When CHA eye drops (bid) were given to normal New Zealand rabbits, surprisingly an incremental increase of TM outflow facility was observed at 30 days compared to day 1 [17]. Most importantly, Phase 2b safety and efficacy clinical trials of Trabodenson (A1R) in patients with POAG/OH have showed a similar pattern of an increased IOP reduction over time, subsequently resulted in a dose switch from BID to QD at week 12 (Data source: Inotek IPO, Feb. 2015). Of note, in glaucoma clinic, most patients with advanced disease eventually have to rely on aggressive drainage surgeries such as trabeculectomy and tube shunt, because current ocular hypotensive drugs, even with combination of 2-4 bottles are still not enough to lower the IOP at individual target level. Why? Trabecular meshwork aging is a serious problem especially in patients with open angle glaucoma, with which contractible TM tissues gradually lose the elasticity and become rigid and thickening over time. While most IOP lowering drugs depend upon natural healthy outflow drainage system to exert their biological and pharmacological effects. As indicated earlier, A1R mediated MMP activations could spur up the enzymatic cleaning and self-renewal of ECM within TM, therefore Trabodenson (A1R) might offer unique therapeutic potentials to restore nature outflow dynamic in patients with glaucoma, in particular of steroid induced glaucoma or ocular hypertension for which abnormal ECM disposition in TM is the predominant pathology.

4. Parainflammation in Glaucoma and Retina Disease Management

4.1: Rescula & Parainflammation in Glaucoma

Ancient Chinese medicine proclaimed the importance of balancing physiological functionality and hemostasis among different compartments of tissue organ in the body. Para-inflammation is a tissue adaptive response to noxious stress, or aging oxidation or malfunction, and has characteristics that are intermediate between basal and acute inflammatory states [18]. In the eye, para-inflammation contributes to the initiation and progression of a large spectrum of significant chronic medical conditions, such as complement factors in dry AMD, persistent DME, IOP independent risk factors in glaucomatous neuropathy, bleb fibrotic failure in trabeculectomy, late onset cornea transplant rejection and uveitic macular edema. There are two new major movements that are worth to mention. First, new appreciation of rescula (unoprostone isopropyl) for its unique anti-inflammatory activity through newly discovered mechanism of B-K channel activation is enlightening possible roles of aging oxidation induced parainflammation in glaucoma pathological process. Based on author's investigation into its molecular traits, unoprostone isopropyl or Rescula belongs to the "Prostone" family of a naturally occurring unsaturated docosanoic fatty acid in the body, its activation of B-K channel and subsequent restoring of cellular membrane hemostasis has multiple pharmacological and clinical implications, such as regulating vascular smooth muscle tones and relaxing contractibility of trabecular meshwork complex, and modulating innate parainflammatory responses. Early clinical evidences are suggesting that rescula might offer a unique benefit to patients with refractory glaucoma and NTG as well as a role in halting the degenerative process in patients with RP, for all of which currently there is no effective treatment available [19-21]. The second new movement is a rising wave of low dose steroid sustained release implants (Ozudex and Iluvien) that are beginning to fulfill its potentials of alleviating chronic parainflammation in patient with refractory DME. Details please see the following *Section*.

4.2: Steroid & Parainflammation in Refractory Macular Edema

There are two proactive water or fluid pump systems in the retina, which help to maintain the dynamic balance between fluid "in and out" across the blood-retina barrier in normal human eyes. In the outer retina, RPE and Bruchs membrane form the primary blood-retina barrier that regulates metabolic and fluid exchange between neural sensory retina, especially photoreceptor layers and its underlying choroid vascular circulation. This pump is the primary driven force responsible for subretinal fluid drainage in various edemous conditions (e.g. DME and CNV). Aging, oxidative damage and chronic inflammation may cause the pump dysfunction and blood retina barrier breakdown, which subsequently results in fluid accumulation in the subretinal retina space. The role of anti-VEGF therapies is to reduce extracellular fluid production by inhibiting vascular permeability or leakage, but does not address the root causes of pump failure. It is commonly believed that the chronic inflammation underpinning clinical DME involves a cluster of inflammatory cytokines such as TNFa, NF-KappaB, interleukins, prostaglandins, bradykinins other than VEGF alone. On the other hand, within the inner retina layer, Muller glia is ensheathed with retina arterioles forming a close physiological proximity that allows for metabolic fluid exchange between retina neurons (not including photoreceptors) and retina blood circulation, and its end-feet has high potassium conductance

[22,23]. Indeed Muller glia cell is a newly recognized water pump that is responsible for fluid drainage and hydraulic conductivity at inner retina. Recent evidences also suggest that Muller glia cell has membrane receptors for corticosteroid such as triamcinolone [24]. This may explain why Iluvien is effective to refractory DME, especially to those who have developed persistent intraretinal cysts (fluids). Therefore, regulation of Muller glia volume has great importance for the homeostasis of extracellular space volume under conditions of intense neural activity (e.g. DR and glaucoma) [24].

Over the past decades, despite the high incidence of ocular side effects (cataract and IOP elevation), steroids have been mainstay treatment for ocular inflammation. Unfortunately there isn't any pathway-based specific target available in clinic yet. A new surge of low dose sustained release steroid delivery such as Ozudex and Iluvien is opening a great prospect for refractory DME, in which parainflammation becomes the predominant pathological entity especially in advanced disease stage. It should be noted that Iluvien is the second-generation intravitreal implant containing fluocinolone acetonide (0.19 mg/3 years, via 25G), which was recently approved for the treatment of DME in the USA. Prior to the FDA approval, Iluvien has also been approved in 17 other countries outside of USA. Compared with Ozudex (23G, 0.7mg dexamethasone/6 weeks), Iluvien is more cost effective with the benefits of less frequent injection and fast wound healing, thus, less risk of surgical complication. This is especially important to diabetic eyes. Of note, the first generation Retisert (high dose, 0.59 mg/3 years) was sutured through pars plana right behind the lens, which caused severe and undesirable IOP elevation and cataract problems in patients with uveitis. Whereas Iluvien is via minimally invasive 25G injector (no suture required), which allows implant reaching to the posterior vitreous cavity, further reduces the incidence and severity of cataract and IOP elevation in DME patient (pivotal FAME trials) [25].

5. Minimally Invasive Sustained Ocular Drug and Gene Delivery

Treating eye disease especially posterior segment eye disease is about delivery (on target). A good drug delivery system can help leverage efficacy and safety at many levels. For example, the total drug loading of Iluvien is 0.19 mg, which is equivalent to 2 eye drops but lasts 3 years. If a patient is given eye drops formulation for 3 years, how many thousand times more of the drug would the patient have to take in order to achieve similar target tissue concentration in the retina? Further we ask the question, "does eye drops work for AMD?" Yes or No, it depends on individual drug, namely, its chemical and physical properties pertinent to target site of action. Despite the fact that more than 80% of the eye drops are immediately lost through nasal lacrimal duct upon instillation, it should be noted that there are three major routes for a single eye drop entering into the intraocular space whilst navigating different ocular tissue barriers. First, eye drops have to penetrate through cornea epithelium layer prior to reaching to the anterior chamber. Second distribution is through cornea limbal-scleral zone, where ciliary long blood vessels enter into the ciliary body. This vascular rich zone poses a relatively thin and weak drug delivery barrier. Most glaucoma IOP lowering drugs take the advantage of this significant channel zone. The third distribution is through trans-sclera route. Of note, sclera surface counts for 90% of ocular surface area. Emerging evidences have showed that sclera is much more permeable than what we thought before. To a certain hydrophilic drug, the 5-9mm thick sclera may render equivalent permeability to the monolayer cornea epithelia layer [26-28]. That's the reason for us to believe that eye drops might work for AMD. Yet, many pharmaceutical molecules or drugs may encounter additional or even bigger challenges while reaching towards the blood-retina barrier prior to landing at a subretinal space.

In recent years nano particle based therapeutic delivery along with subretinal and superachoroid delivery routes begin to merge. The first LCA (Leber congenitor amaurosis) clinical trials (2008) pioneered by groups at University of Pennsylvania and University of College London (UCL) have adapted a minimally invasive subretinal delivery system (Retinaject, SurModics), which has achieved great surgical outcome along with biological safety and promising efficacies [29,30]. On the other hand, Clearside Bio (GA) is pioneering superachoroidal delivery via a short micro needle directly reaching to fenestrated superachoroid space [31]. Through this route, therapeutic target can directly reach to the inner layer of choroid microcapillary bed behind the RPE layer posteriorly, which could be very useful for retinal gene delivery preferably targeting on the RPE cells (e.g. LCA2 on RPE65 mutation). As such, superachoroidal delivery allows for a large area of RPE to be genetically transfected, compared to a very small subretinal "bleb" if via sub retinal delivery. Due to improved pharmacokinetics and reduced IOP and cataract issues, superachoroidal delivery may also extend a new life to triamcinolone that is currently used as off label via intravitreal injection for the treatment of DME.

6. Bio-therapeutic Innovation at a Glance

Bio-therapeutics represents a new trend of future medicine development taskforce. By 2050, an estimate of 60% pharmaceutical pipelines will be “bio” based therapeutic intervention. The landscape of bio-therapeutic innovation is very broad, from gene therapy to stem cell regenerative medicine; from protein/peptide and antibody drugs to emerging RNA based therapeutic strategies. The concept of gene therapy also has evolved from conventional gene replacement for the treatment of genetic diseases to genetic based sustained protein delivery for non-genetic retinal diseases, e.g. AAV-sflt-1 for wet AMD (Avalanche Bio). Following initial clinical success of adeno-associated virus (AAV) mediated gene therapy for LCA (Phase 3), new generation of viral vector mediated gene replacement for RP and SMD are the highlights for possible early intervention to diseases with well-defined genetic mutations such as MYO7A Usher1B/RP (if safety is warrant). Sanofi/Oxford Biomedica and Regenx Bio are major players in this field. Editas Medicine (MA) is the newest member in gene therapy family that is pioneering CRISPR technology platform. Although the technology is still in its early infancy, it offers great potential for precision medicine in the future. Micro RNA and messenger RNA (Mordena Therapeutic) therapeutic platforms could serve as a long-term protein drug delivery alternative, yet they are also at early stage infancy. Challenges of intracellular delivery and precise control of RNA based cascade regulations must take into account for translational development and validation in both preclinical and clinical settings. Quark Therapeutics has made a step earlier in SiRNA based therapy with clinical candidates for DME and optic neuropathy (Phase ½).

In a competitive landscape, stem cell replacement is a younger cousin of gene replacement therapy. Following extensive scientific exploration in the early days [32,33], the field is now quickly catching up with rising wave of ES cell or induced pluripotent stem cell (iPS) derivative cellular transplant, lineage specific neural stem cell therapy and blood born stem cell therapies, which are opening broad exciting promises for neural protection, tissue rejuvenation and photoreceptor/RPE replacement. Ocata Therapeutic (MA), Stem Cell Inc. (CA), J&J Stem Cell Venture (PA), ReNeuron (UK) and Kyoto Univ. (JP) are using different donor sources to address RPE and photoreceptor cell loss in patients with AMD, SMD and myopic macular degeneration. Compared to neuronal cell replacement, blood born stem cell therapy could potentially embrace a unique advantage of using autologous source. For example, Betastem Inc (CA) is developing TGF-beta RNAi based autologous blood born stem cell therapy (via intraocular delivery) for diabetic retinopathy (pre-IND stage).

In artificial retina domain, Second Sight is successfully paving the clinical regulatory path for electrical stimulation based Argus II retinal prosthesis called “bionic eye”, which was received the FDA approval in the early 2013 [34]. Boston Retinal Implant is developing ultra-thin subretinal electrical prosthesis (IND stage), which might offer a closer proximity to normal visual functional processes compared to epiretinal prosthesis. Lambdavisision (CT) is pioneering a new generation protein-based artificial retina implant for end-stage retinal degenerative diseases such as RP and AMD. The implant contains non-bioactive polymer scaffold and multiple layers of photo-sensitive bacteriorhodopsin (BR) protein, which has demonstrated unprecedented thermal and chemical stabilities in vitro [35]. Proof of concept study conducted on ex-vivo degenerative retinal flat mount tissue has showed that under office light stimuli, BR implant is able to drive the remaining ganglion cell firing at the absence of photoreceptor layers (data was presented at Eye-2015 International Conference on July 13-15, 2015 in Baltimore, USA). Preclinical biocompatibility, safety and efficacy studies are in progress.

7. Strategic Insights and Future Solutions

7.1: Bridging Gaps for Translational Therapeutic Innovation

In pharmaceutical industry, developing a new drug takes about 10-12 years and \$1.0 billion in order to bring a viable drug to the market, unfortunately there are still 90% failure. My recent thorough investigation has led to in-depth understanding of this dilemma, which may further enlighten an effective translational path finding approach toward more successful clinical development taskforce. Figure 3 has mapped out two big gaps that most drugs fail on translational development and validation. The first gap is from pivotal preclinical to early stage clinical development with about 60% failure, either on safety and/or efficacy. The second gap is at translational development from early stage (Phase ½) towards mid-late stage (pivotal Phase 3 trials) with about 30% failure, either on safety and/or efficacy. What are the key risk factors? First of all, there are 4 main inherited limitations or factors that attribute to the early stage translational failure (60%). a) disease root causes are not clear or complicated in nature. b) lack of surrogate biomarkers.

c) limitations on animal models. d) insufficient drug delivery system (off target). While moving towards mid-late stage translational development, we face greater complexity of disease staging and pathological phenotype, lack of global strategic thinking often leads to “generic” clinical protocol and study design. Without integrative knowledge about disease pathophysiological entity and molecular traits of a tested drug, it is unlikely to put the basic principles of “giving the right drug to the right patient at the right time” into a meaningful practice. This may explain the 30% failure at bridging the 2nd gaps of clinical translation. In terms of stem cell and gene therapy as well as other cutting-edge bio-therapeutic innovation, it is the “gulfs” (not gaps) that we need to across because many cutting-edge technologies and therapies are still at early stage or infancy for clinical application; nevertheless they represent an exciting future of modern medicine taskforce.

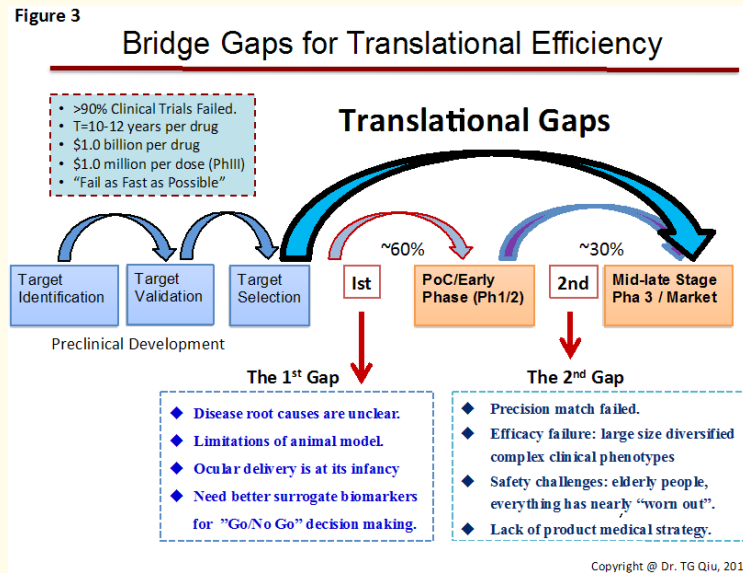


Figure 3: Bridging Gaps for Translational Efficiency. Presented at MassBio Signature Event on October 17, 2012, Cambridge, USA.

7.2: Therapeutic Product Development is Building a Pyramid

Academic research is like cultivating a garden and always on the ground zero, whereas pharmaceutical drug development is building a pyramid (Figure 4). There are only two questions that we must answer: *does it work? Is it safe?* In order to get there, first of all, we need to have “know-how” skills to exercise “precision-match” between target MoA (mechanism of action) and disease staging/sub-phenotype. This is the golden rules, which apply to everywhere from product concept initiation to post-marketing treatment algorithm. Secondly, dosing and drug delivery (on target) are the key tactics that further defines the two leading questions pertinent to treatment effectiveness and drug safety profile. The goal is to capture right dose window whilst eliminating off target. Finally and most importantly, creating product medical strategy is a must step which defines the content of future regulatory labels. Traditionally, product medical strategy is at post-marketing arena after the completion of Phase 3 pivotal clinical trials. With increased global competitive landscape and disease complexity, it’s strongly recommended that medical product strategy should be in place before Phase 3 clinical patient enrollment. Because this helps to map out drug treatment responders (niche indication), capture comparative endpoints, and further streamline clinical development strategy and study design (superiority vs inferiority). If we can well master these golden rules, tactics and strategies, we shall be able to win a battle without a fight!

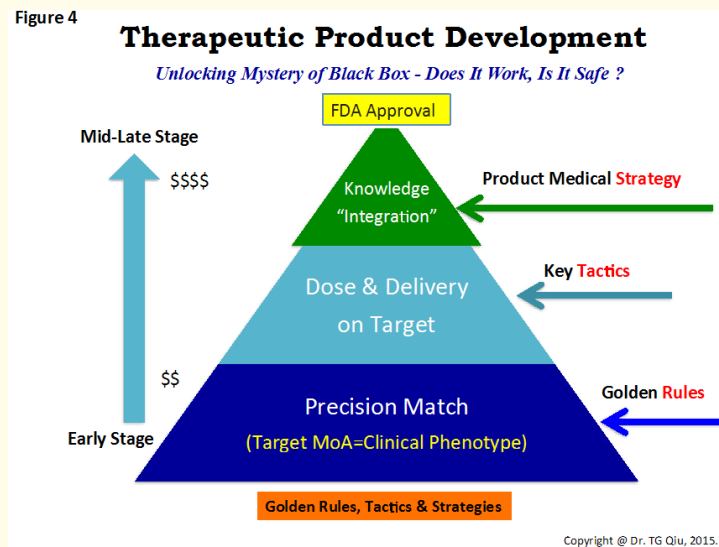


Figure 4: Golden Rules, Tactics and Strategies for Therapeutic Product Development. Presented at Eye-2015 International Conference on July 13-15, 2015, Baltimore, USA.

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Financial Interests

Tina Guanting Qiu, MD PhD is an independent ophthalmic executive consultant for Inotek Pharmaceuticals, MA, and LambdaVision Inc., CT. Previously Dr. Qiu was Chief Medical Officer at BetaStem Inc., Clinical Ophthalmology Expert Consultant for Ocata Therapeutics, MA, Field Medical Consultant for Sucampo Pharma Americas LLC through MDea Inc. NY, Ophthalmic Consultant Surgeon for SurModics Inc., CA, and Biomedical Council Member at Gerson Lehrman Group.

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