QLT Inc
Rationale and Background for the development of QLT091001
(Note: QLT091001 is not approved for commercial use in any countries, worldwide)

Introduction

QLT Inc. (QLT) is a Canadian company focused on developing innovative ocular products. QLT091001 is an oral synthetic retinoid proposed as a potential treatment for retinal diseases caused by gene mutations that interfere with the availability of 11-*cis*-retinal.

QLT091001 is being developed for two separate inherited orphan drug retinal indications:

- Leber Congenital Amaurosis (LCA) due to mutations in lecithin: retinol acyltransferase (*LRAT*) and retinal pigment epithelium protein 65 (*RPE65*)
- Retinitis Pigmentosa (RP) due to mutations in *LRAT* and *RPE65.*

Both LCA and RP are severe and debilitating inherited conditions for which no suitable approved treatment in North America exists to date. Both conditions lead to blindness and compromised quality of life in patients. Both of these indications qualify for orphan drug status and in the United States, orphan drug designation was received in December 2010. In February 2011 the European Medicines Agency (EMA) Committee for Orphan Medicinal Products (COMP) provided positive opinions for two distinct orphan drug designations for LCA and RP .

Disease Characteristics of LCA and RP

Leber Congenital Amaurosis

LCA is a devastating, rare, hereditary disease and is considered the most severe form of all retinal degenerative diseases. Characteristics of LCA include severe visual impairment at or soon after birth (causing childhood blindness), wandering nystagmus, abnormal pupillary responses (amaurotic pupils), a severely reduced or abolished electroretinogram (ERG), and significant hyperopia (farsightedness) (Hanein et al. 2004; Zernant et al. 2005). One third of all patients have no light perception.

The diagnosis of LCA is established by clinical findings as described above; especially diagnostic is the absent or near-absent response to full flash ERG (Hamel 2006; Dharmaraj et al. 2000). Molecular genetic testing is clinically available for the 12 genes currently known to be associated with LCA (Weleber et al. 2010).

LCA exhibits clinical and genetic heterogeneity in terms of the natural history of vision loss, behavior in low light conditions, and genetic defects responsible for the phenotype (Berger et al. 2010).

LCA can be classified by disease pathway and gene mutation, as follows (Berger et al. 2010):
• Retinoid cycle (*LRAT*, *RPE65, RDH12*)
• Phototransduction pathway (*GUCY2D* and *AIPLI*)
• Photoreceptor development (*CRB1* and CRX)
• Ciliary protein trafficking (*CEP290*, *RPGRIP1*, *LCA5*, *TULP1*)
• Regulation of cell growth (*IMPDH1*)
• Transcription and splicing (*RD3*)
• RPE phagocytosis (MERTK)

Genetic testing is now able to determine the genotype in approximately 70% of cases, depending on the study and cultural background of the population. For example, eight genes contain 70% of the mutations in LCA cases tested in the US (Stone 2007). To date, mutations in a total of 16 genes have been identified to cause about 70% of worldwide LCA cases, but these do not account for all cases of LCA as 30% of LCA patients harbor mutations in genes that remain to be identified (Rob Koenekoop, pers com March 2011; den Hollander et al. 2008; Berger et al. 2010; Estrada-Cuzcano 2010). Mode of inheritance for LCA is primarily autosomal recessive (AR), with only 2 of the identified target genes (*CRX* and *IMPDH1*) inherited by the autosomal dominant (AD) mode (Berger et al. 2010). Mutations in *CRX* and *IMPDH1* are extremely rare.

Retinitis Pigmentosa
RP is a group of debilitating inherited disorders in which abnormalities of the photoreceptors (rods and cones) or the retinal pigment epithelium (RPE) lead to progressive visual loss (Pagon & Daiger 2005). Kannabiran (2008) characterizes RP as "one of the major forms of incurable blindness in the world." Kannabiran (2008) further describes RP:

> It is a progressive disorder involving the death of rod photoreceptors followed by the loss of cones; although the loss of both types of photoreceptors can occur simultaneously. Although the course and progression of the disease show considerable variation between individuals, it is typically characterized by initial symptoms of night blindness, with onset in adolescence or early adulthood, loss of peripheral vision and, as the disease progresses, loss of central vision leading to complete blindness or severe visual impairment.....
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> The age-at-onset of symptoms is highly variable and ranges from childhood to mid-adulthood. Electroretinographic (ERG) responses are an early indicator of loss of rod and cone function in RP and diminution of ERG responses can be evident within the first few years of life, even though symptoms appear much later.

Typical RP presents as primary degeneration of rods (photoreceptors that are sensitive to low light) with secondary degeneration of cones (photoreceptors that detect color, are responsible for all high-resolution vision, and are less sensitive to light than rods) and is

consequently described as a rod-cone dystrophy, with rods being more affected than cones.

RP usually has only ocular effects, but 20-30% of patients have associated non-ocular disease; these cases represent more than 30 different syndromes (Hartong et al. 2006) and are referred to as syndromic RP. The 2 main types of syndromic RP are Usher's syndrome (10-20% of RP cases) and Bardet-Biedl syndrome (5-6% of RP cases) (Kannabiran 2008; Hartong et al. 2006):

Current Treatment Options for LCA and RP

Leber Congenital Amaurosis

As of May, 2011, there are currently no approved drug treatments for LCA. Gene therapy for *RPE65*-related LCA is under investigation in trials in the U.S. and the UK (Musarella & MacDonald 2011; see also http://www.clinicaltrials.gov: NCT00481546 and NCT00643747).

Patients with LCA usually receive genetic counseling, referral to programs for the visually impaired, and general support in the form of regular medical follow-up for ophthalmic assessment of vision, and in those with residual vision, possible presence of amblyopia, glaucoma, and cataract.

Patients with LCA benefit from correction of refractive error, use of low-vision aids when possible, and optimal access to educational and work-related opportunities. Children with LCA are discouraged from repeatedly poking and pressing on their eyes.

Retinitis Pigmentosa

As of May, 2011, currently under investigation are neurotrophic factors such as ciliary neurotrophic factor (CNTF), and retinal transplantation (Musarella & MacDonald 2011). Recently, a retinal prosthesis for the blind, Argus II Retinal Prosthesis System ("Argus II") was approved for sale in the European Economic Area (EEA). The manufacturer, Second Sight, evaluated the efficacy and safety of the Argus II system in patients with RP. Additional information can be found on the company's website: http://www.2-sight.eu/ee/home

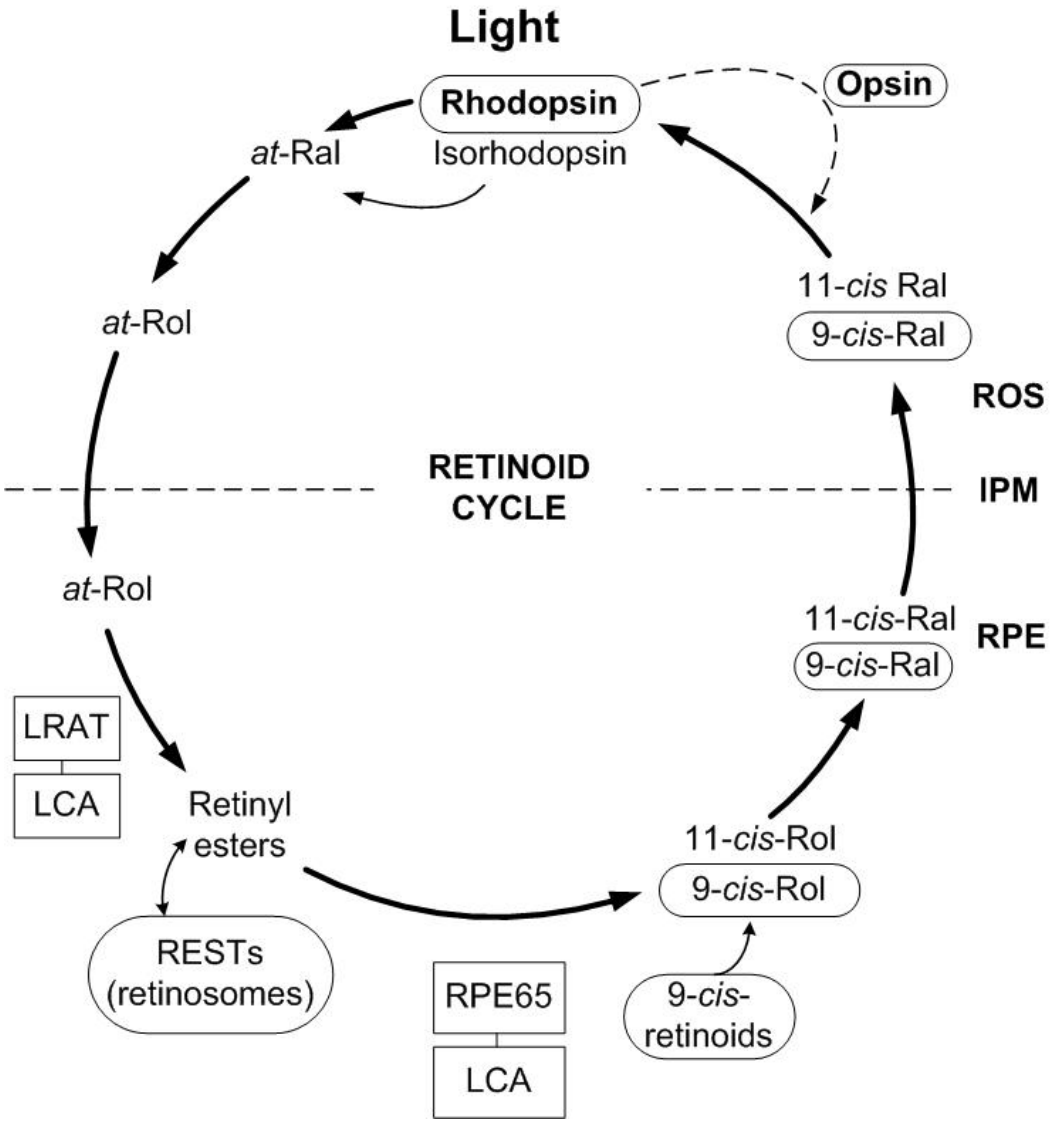
Treatment of patients with RP primarily involves genetic counseling, and general support such as information and regular medical follow up. The limited range of current therapeutic approaches are restricted to attempts to slow down the degenerative process by sunlight protection and vitamin supplementation, treating complications (cataract and macular edema), and helping patients cope with the social and psychological impact of blindness(Hamel 2006)

LCA, RP and the Visual Cycle

As discussed above, QLT091001 is being developed for LCA and RP due to mutations in *LRAT* and *RPE65*. Mutations in *LRAT* and *RPE65* result in the absence of 11-*cis*-retinal, an important molecule essential for vision. 11-*cis*-retinal is produced in the retinal pigment epithelium (RPE) and binds to the protein opsin to form rhodopsin in the rod outer segment.

Vision is initiated when a light photon is captured by 11-*cis*-retinal, resulting in isomerization to all-*trans*-retinal and dissociation from opsin. Vision is sustained by the cycling of all *trans*-retinal back into 11-*cis*-retinal, which occurs by a complex series of biochemical reactions involving multiple enzymes and proteins in the retinoid cycle. Figure 1 depicts this process, along with the enzymes and proteins involved.

Figure 1



Rationale for QLT091001

The therapeutic strategy with QLT091001 is to facilitate recovery or restoration of visual function by acting as an analogue replacement for missing 11-*cis*-retinal and restoring the key biochemical component of the visual (retinoid) cycle. QLT091001 is an orally available synthetic prodrug that is converted to 9-*cis*-retinal, which forms the visual pigment isorhodopsin (instead of the usual rhodopsin formed from 11-*cis*-retinal). Isorhodopsin is a functionally active pigment in the visual cycle that undergoes conformational changes through the same photoproducts as 11-*cis*-retinal-regenerated rhodopsin.

In humans with a deficiency in 11-*cis*-retinal, isorhodopsin may act as a suitable substitute for rhodopsin in the visual cycle (Van Hooser et al. 2002; Maeda et al. 2006). This therapeutic strategy is supported by studies in *Rpe65*-deficient mice that detected a restoration of ERG measures after supplementation with 9-*cis*-retinal (Van Hooser et al. 2002; Van Hooser et al. 2000; unpublished data). Similarly, long lasting restoration of retinal function in deficient mice was seen with increased ERG responses from 5 to 50% when treated with 9-*cis*-retinal (Van Hooser et al. 2000).

Increases in psychophysical and pupillometry responses in dogs with defects in *RPE65* have also been observed after treatment with subretinal adeno-associated virus (AAV) (Acland et al. 2001), further supporting the rationale for a therapeutic mechanism based on biochemical intervention.

This therapeutic strategy is also supported by human studies and QLT has obtained promising early Phase Ib data in LCA patients with *LRAT* and *RPE65* mutations, suggesting the product may affect various parameters of visual function and daily quality of life in pediatric and adult patients. Preliminary data in a small open-label study has shown that some patients had improvement in visual function parameters with a long duration of effect. However, as with all drugs at the Phase I stage of development, these preliminary results need to be substantiated in larger safety and efficacy studies in the future.

It is important to note that several gene defects have been linked to LCA and RP, and not all may be appropriate targets for therapy with QLT091001. The genes that result in biochemical defects for which therapy with QLT091001 may provide benefit include *RPE65* and *LRAT*. Estimates have reported that in the LCA population, less than 10% of patients have a mutation in either the RPE65 or LRAT genes (Lotery et al. 2000; Thompson et al. 2001; Hanein et al, 2004; Koenekoop 2004; Senechal et al. 2006; Sweeney et al. 2007; den Hollander, et al. 2008; Kantar Health; 2010). In the RP population, <5% have RPE65 or LRAT mutations (Gu et al. 1997; Morimura et al. 1998; Ruiz et al. 2001; Thompson et al, 2001; Senechal et al. 2006; den Hollander et al., 2007; Kantar Health; 2010).

Future Direction

QLT continues the Phase 1b clinical proof-of-concept study of QLT091001 in patients with LCA and RP. The study is ongoing and continues to enroll patients. Results from patients in the LCA cohort are expected in the second quarter of 2011. Please refer to the ClinTrials.gov website for more information

http://clinicaltrials.gov/ct2/show/NCT01014052
Clinical trial registry number: clinicaltrials.gov: NCT01014052
Human subjects: in compliance with Declaration of Helsinki

QLT also continues to work with international regulatory authorities to develop this Orphan Drug product globally. Plans are currently underway for future studies in global centres.

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