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Developmental approach towards high resolution Optical Coherence Tomography for Glaucoma diagnostics

Björn Kemper¹; Steffi Ketelhut¹, Peter Heiduschka², Marie Thorn³, Michael Larsen³, Jürgen Schneckeburger^{1*}

¹Biomedical Technology Center of the Medical Faculty, University of Muenster, 48149 Muenster, Germany

²Department of Ophthalmology, University of Muenster, 48149 Muenster, Germany

³Department of Ophthalmology, Rigshospitalet Glostrup, 2600 Glostrup, Denmark

Corresponding author: *schneckeburger@uni-muenster.de

Abstract

Glaucoma is caused by a pathological rise in the intraocular pressure, which results in a progressive loss of vision by a damage to retinal cells and the optical nerve head. Early detection of pressure-induced damage is thus essential for the reduction of eye pressure and to prevent severe incapacity or blindness. Within the new European Project GALAHAD (Glaucoma Advanced, Label free High Resolution Automated OCT Diagnostics), we will develop a new low-cost and high-resolution OCT system for the early detection of glaucoma. The device is designed to improve diagnosis based on a new system of optical coherence tomography. Although OCT systems are at present available in ophthalmology centres, high-resolution devices are extremely expensive. The novelty of the new Galahad system is its super wideband light source to achieve high image resolution at a reasonable cost.

Proof of concept experiments with cell and tissue Glaucoma test standards and animal models are planned for the test of the new optical components and new algorithms performance for the identification of Glaucoma associated cell and tissue structures. The intense training of the software systems with various samples should result in a increased sensitivity and specificity of the OCT software system.

Key words: Optical Coherence Tomography, Glaucoma, Glaucoma cell and tissue standards, image analysis algorithms

1. INTRODUCTION

The aim of this document is the identification and definition of test standards for UHR-OCT and polarization sensitive UHR-OCT. The document will define requirements and specifications for GALAHAD biological test standards. Key features are optical properties close to Retina properties and structures as well as a sufficient stability for repeated measurements and continuous benchmarking during the course of the project.

This report presents available and possible in vitro and in vivo models for Glaucoma OCT development as well as the advantages and disadvantages regarding the GALAHAD requirements. A selection of in vitro and in vivo Glaucoma models will be tested for standardization and as possible tool for benchmarking.

At least two in vivo models, the Endothelin-1 rat model and DAB/2J mice will be used for the project.

The development and performance of the GALAHAD technical components will be analyzed by using standardized biological samples, which are stable over time or can be reproducibly prepared. These standards allow the comparison and benchmarking of the novel technologies to state of the art systems and improvements within the project.

The clinical GALAHAD partners have selected model systems representing 2D and 3D glaucoma related structures for the performance characterization of the GALAHAD system components and algorithm training. From simple 2D cell culture systems to 3D models including 3D phantoms and cryostat fixated, paraffin-embedded tissue sections from glaucoma rodent animal models, and finally living animals for gathering different model systems, are tested for the suitability as standards for the high resolution OCT system.

2. RESULTS

The following requirements for test standards were defined:

- Suitable resolution and performance testing of UHR OCT and polarization sensitive OCT
- Standards should reflect glaucoma relevant tissue properties concerning structures and dimensions
- Standards should represent typical optical properties as refractive index properties and birefringence parameters
- Stability of the test standards should be sufficient to allow exchange between partners for performance testing of different OCT systems and system components at different locations
- Properties of the standards should be suitable for performance testing of developed OCT components and OCT system during the different development steps
- Detected OCT signals from standards should be suitable for performance testing of the developed algorithms

Target parameters of test standards for UHR-OCT performance testing

Considering results of baseline studies on the current state of the art in OCT and polarization sensitive OCT available test standards have been defined:

1. Target parameters: Considering the currently achieved resolution of commercially available OCT systems and publications on recently developed UHR-OCT systems, test standards should reliably reflect the achievable state of the art resolution (see also the GALAHAD document Baseline Studies):
 - a. Lateral resolution: $\approx 1 \mu\text{m}$
 - b. Axial resolution: $\approx 1 \mu\text{m}$
2. Moreover, the test standards should reflect tissue properties:
 - a. Tissue layer thickness of the retina
 - b. Refractive index properties of the eye tissue
 - c. Birefringence properties of the eye tissue
3. Stability properties:

- a. Samples should be stable for several months allowing performance tests of UHR-OCT systems in different project stages
- b. Geometric dimensions and optical properties of the standards should match the capabilities of experimental OCT setups

In vitro 2D and 3D Glaucoma models			
Modell	Advantages	Disadvantages	GALAHAD use
PC12 nerve cells	Homogeneous, standardized, established cell culture conditions	Thin one layer structure, only one dimension, no Glaucoma relevant structures	Back up model for dissected retina tissues
BV2 microglia cells	Homogeneous, standardized, established cell culture conditions	Thin one layer structure, only one dimension, no Glaucoma relevant structures	Back up model for dissected retina tissues
MDCK epithelial cells	Homogeneous, standardized, established cell culture conditions	15 μm one layer structure, only one dimension, no Glaucoma relevant structures	Back up model for dissected retina tissues
3D phantoms of collagen and agar layers containing cells	Adjustable highly standardized structures	No Glaucoma relevant structures	Back up model for GALAHAD OCT system resolution testing
3D phantoms of collagen and agar layers defined micro-particles up to 3 μm	Adjustable highly standardized structures	No Glaucoma relevant structures	Model for GALAHAD OCT system resolution testing
Commercial differentiated 3D cornea models (EpiCornea, Mattek Corp., Ashland, USA)	Highly standardized 3D structures	No Glaucoma relevant tissues	Possible in vitro back up model
Dissected retina tissue from Glaucoma animal models	Available, stable after fixation, long term use	Development of preparation methods	Standardized in vitro Glaucoma model

Table 1: Summary of available in vitro Glaucoma models for GALAHAD system development and testing.

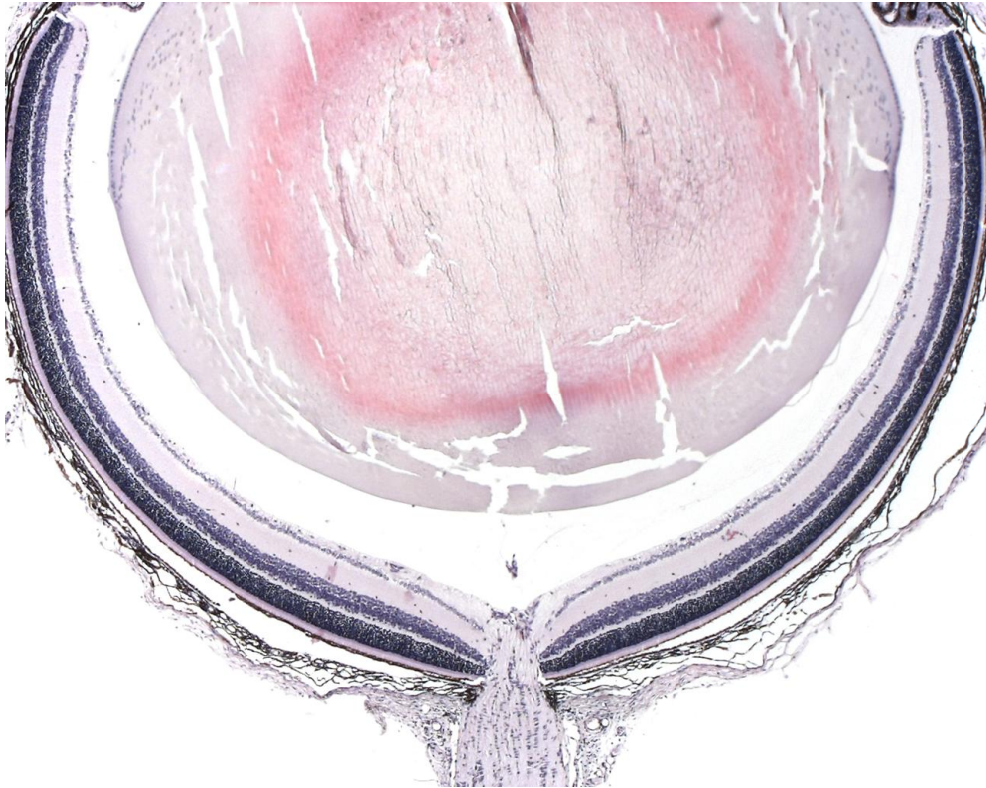


Figure 1. HE stained section of a mice eye.

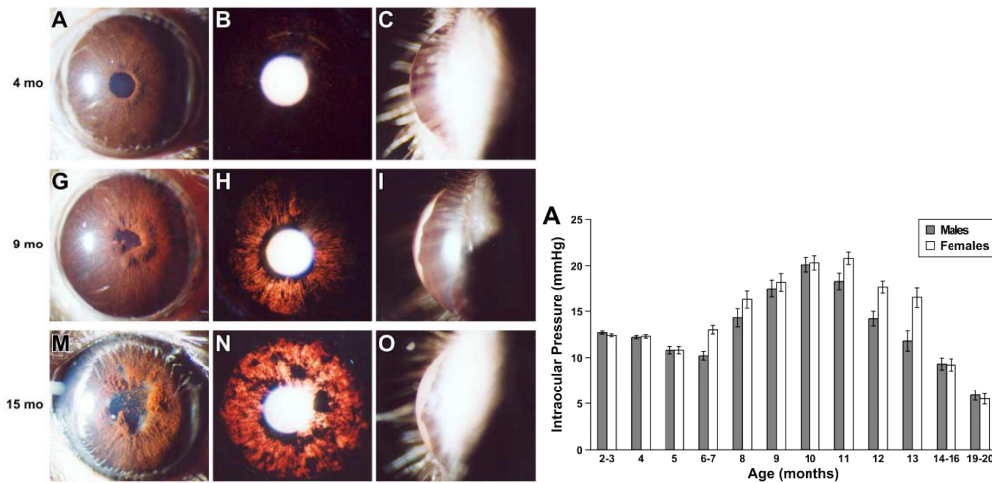


Figure 2: Appearance of the DBA/2J mouse iris undergoing iris pigment dispersion (left) and development of enhanced intraocular pressure at months 8 to 10 (Libby *et al.*, 2005).

In vivo Glaucoma models			
Model	Advantages	Disadvantages	GALAHAD use
Healthy rabbits	Easy accessible large eyes	No Glaucoma structures, eye geometry differs from rats and mice	Established model
Healthy male Sprague Dawley rat	Easy accessible, established model	High frequencies of heart beat and breathing inhibit repeated scans	Established model
Endothelin-1 (ET-1) rat model	Retinal ischemia assessed on days 3,7,14 after injection	Only slight changes since only a few cells of the retinal layers are damaged	GALAHAD Glaucoma model
DBA/2J mice.	Established model for glaucoma research, develop a pigment dispersion syndrome	First Glaucoma symptoms after 8 to 9 months	GALAHAD Glaucoma model
Intravitreal injection of glutamate solution in mice	Acute Glaucoma model	Difficult to apply, high dropout rate	Back up Glaucoma model
Optic nerve section in mice	Acute Glaucoma model	Changes in 3D structures differ from	Back up Glaucoma model

Table 2: Summary of available in vivo Glaucoma models for GALAHAD system development and testing.

3. CONCLUSION

The GALAHAD biomedical partners have defined requirements and target parameters for biological GALAHAD Glaucoma standards for the testing and benchmarking of the GALAHAD technical developments. A variety of in vitro and in vivo 2D and 3D cell, tissue and animal Glaucoma models were evaluated for a possible use in GALAHAD. The GALAHAD partners will further test selected in vitro and in vivo models for performance as test standards and benchmarking tools. Glaucoma models fulfilling the described requirements will be used within the project for system and algorithm performance evaluation and benchmarking.

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