2014 Presidential Fellowship Proposal

Development of a Handheld OCT Probe for Guiding 25 Gauge Vitrectomy
(안과 망막 정밀수술용 3 차원 영상 프로브)

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Research Project Outline

Vitrectomy is a surgical procedure in which the vitreous humor, the gel-like fluid in the eye, is removed and can prevent blindness due to several medical conditions and diseases. Vitrectomy is performed by inserting a fluid cannula and two needle-sized surgical tools, one of which a light source and the other a removal tool. Currently, the surgeon performs surgery by looking through the patient's dilated pupil to remove the transparent vitreous humor, which makes this surgery extremely difficult. Other means of visual guidance are limited to ultrasonography and 2D endoscopy. In order to perform a sutureless vitrectomy, tools must at least be 20-gauge (at most 0.9mm diameter). This project aims to develop a handheld 3D imaging system based on optical coherence tomography that also images white light and OCT simultaneously, and will 25-gauge (0.5mm diameter) vitrectomy. Succeeding in this project will yield the thinnest reported vitrectomy-guiding 3D endoscope.

Anticipated milestones:

1. Develop a miniaturized OCT integrated with white light microscopy:
   OCT produces 3D images using infrared: object surfaces with its cross section. White light microscopy projects white light, and images like an ordinary camera. The probe will need to be 0.5mm in diameter to qualify, however, the field of view will need to be 4mm in diameter. Goal: to assembly a 0.5mm diameter probe that will simultaneously image 0.4mm diameter of OCT and white light.
2. Optimize system specifications to produce high contrast images of ex vivo tissue:
   Cow eye will be used for image testing. Other animal experiments will be conducted in Asan Medical Center. Goal: tune the system to obtain clinically useful images.
3. Optimize the design according to clinical or surgical specifications
   Commercially available optical equipment are heavy and bulky making the imaging system very large. The imaging device will need to fit comfortably in the hand and be light enough to hold for several hours during the operation. The device must come with software that will allow the surgeon to control the OCT and endoscope. Goal: create a handheld probe that is light and software for user interfacing.
4. Conduct human clinical trials
   Goal: to compare results of vitrectomy with and without this device.

Recommendation Letter

Dear Committee:

I am very pleased to write a recommendation letter for Mr. Calvin Yoon in his application of the Presidential Fellowship. Mr. Yoon is a first year graduate student of integrated biosciences and biotechnology (IBB) just started this January. I met Mr. Yoon last summer when he worked at POSTECH as a summer intern student under the guidance of Prof. G-One Ahn. I was quite curious about Mr. Yoon, because he did his Bachelor's degree in Biomedical Engineering, University of Rochester, US and I thought that he could easily find good positions in the US. Mr. Yoon is a Korean-American, who came to Korea to study more on what he wanted to do: that was biology, tumor biology especially. Mr. Yoon seems to have no problem in entering new fields if that is interesting enough. Mr. Yoon worked in several biology laboratories including the one of Prof. In-San Kim at Kyungpook National University, Department of Medicine, and the one of Prof. G-One Ahn of IBB and Jin Kwan Han of Biology here. Mr. Yoon joined our group to combine his biomedical engineering knowledge in his undergraduate study with his biology experiences to develop new biomedical devices. Mr. Yoon is a kind of person who can bridge gap between technology and bioscience with good understanding on both sides. I also heard that Mr. Yoon has some problem associated with military service by studying in Korea, because he is a citizen of both countries. However, Mr. Yoon seems not being dampened by this complicated situation. Mr. Yoon has an active challenge-seeking attitude, and I am certain that he will make his goals accomplished. The Presidential Fellowship will provide a recognition to support his academic activity and personal life. Therefore, I strongly recommend Mr. Yoon for the Presidential Fellowship.

Best regards,
Ki Hean Kim, PhD

Cover Letter

I am Calvin Yoon, a student passionate about biomedical research and pursuing opportunities that I find challenging. I am writing this cover letter to describe my research abilities to be considered for the 2014 Presidential Fellowship. On May 2013, I received a bachelors of science in Biomedical Engineering with a focus in Cell & Tissue Engineering from the University of Rochester, and during the spring 2012 semester, have studied abroad at the University of New South Wales in Australia.

My research experiences have allowed me to become very familiar with the research environment and the research development process. During the spring of 2010, I assisted Dr. Max Rempel and Dr. Edward Schwarz of the Center of Musculoskeletal Research at the University of Rochester in determining the optimal wavelength at which light-activated gene therapy is targeted to expediting proliferation of nonvascular tissue, such as articular cartilage in the knees. During the summer of 2012, I assisted Dr. So Youn Kim and Dr. In San Kim at Kyungpook National University in South Korea in furthering their studies on the mechanism by which macrophage engulf apoptotic cells by focusing on the stabilin-2 receptor pathway. Cell corpse clearance is an integral part of wound healing. During the summer of 2013, I participated in a research internship at POSTECH hosted by the Interdisciplinary Biosciences and Biotechnology (I-BIO) department. There, under the supervision of Dr. G-One Ahn, I optimized an implantation procedure of intracranial window chamber in mice in order to observe, using two-photon microscopy, microglial activity in stroke-induced mice. This fall of 2013, I conducted research on the affect the TGFb signaling pathway has on cancer metastasis under Dr. Jin Kwan Han of the Life Sciences Department at POSTECH and confirmed that the GTPase Rap 2 may be involved in the ubiquitination of Ak2 receptors in MCF7 early-stage breast cancer cells. Currently, I am a graduate student under Dr. Kihean Kim of the Biomedical Optics Laboratory.

With respect to projects with direct clinical applications, I completed two major projects during my undergraduate year: one of which was an academic project and the other of which was a senior design project. The project for my Biomedical Computation course required that I detect tumorous regions of tissue using a simplified pharmacokinetic analysis of optical contrast agent and extensive image analysis on MATLAB. Additionally, my senior design project involved improving a scanning feedback mechanism of the Gabor Domain Optical Coherence Microscopy (GDOCM) system, with a selective team, to enable high resolution imaging of the skin. GDOCM is a technology developed by our customer, Dr. Jannick Rolland of the Institute of Optics at the University of Rochester. The motivation behind this project was to advance the research on noninvasive skin cancer detection. Furthermore, the project was completed with its next steps set for clinical trials, and our team's project was featured on local Rochester news. Other biomedical engineering skills were developed from course projects that ranged from building affordable pulse oximeters and coding interactive audiometric tests with MATLAB.

In summary, I believe that the diversity of my academic experiences, which fuels my creativity, paired with my aggressive pursuit for research, driven by my devotion to the field, makes me a strong candidate for the Presidential Fellowship. I would be more than happy to share more about my experiences and visions.

Research Contents

Title:

Development of a Handheld OCT Probe for Guiding 25 Gauge Vitrectomy

Purpose:

The purpose of this project is to develop a high-resolution, real-time, handheld 3D imaging system based on OCT, which will guide 25 gauge vitrectomy.

Introduction:

Vitrectomy is a surgical procedure that is involved in correcting the following emergencies of the eye, which may lead to blindness if not treated immediately:

Choroidal neovascularization, choroiditis, diabetic retinopathy, dropped nucleus, endophthalmitis, macular pucker, giant retinal tears, globe perforation, macular holes, macular edemas, posteriorly subluxated and dislocated intraocular lens, tractional, rhegmatogenous, and exudative retinal detachment, retinopathy of prematurity, primary retina telangiectasia, uveitis, vitreous hemorrhage, and cytomegalovirus retinitis [1-17].

Vitrectomy completely or partially removes the vitreous humor, the gel-like fluid in the eye that becomes clouded by blood or tissue debris during these emergencies.

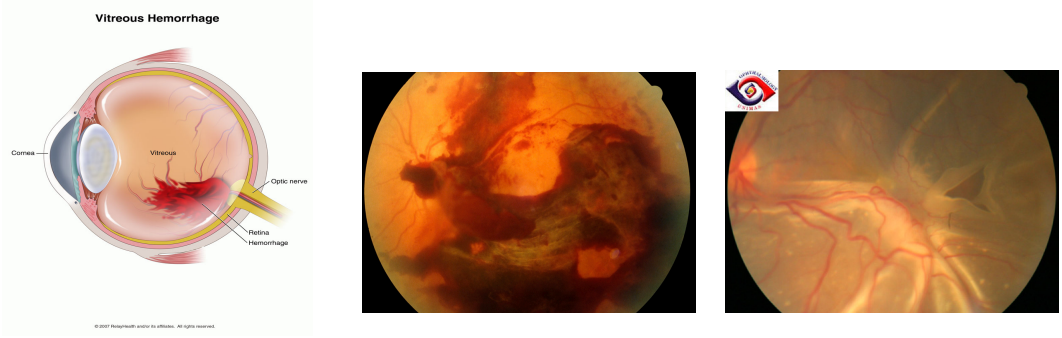

Figure 1. (Left) Illustration of vitreous hemorrhage, the spilling of blood into the vitreous humor. (Center) An image of the vitreous hemorrhage. (Right) An image of retinal detachment. Image search keywords: "vitreous hemorrhage", "retinal detachment".

Vitrectomy is performed by creating three ports into the eye and inserting an infusion cannula, which feeds in substitute vitreous, an endoillumination probe, which illuminates the interior of the eye, and a vitreous cutter, which cuts and removes the vitreous humor. The surgeon has manual control over the location of the endoillumination probe and the vitreous cutter.

Currently, the surgery is performed plain sight through the pupil with the occasional assistance of wide-angle viewing contacts, pupil dilator, or a microscope. In the event that the vitreous humor clouds densely to occlude viewing of the retina, ultrasonography may be used to locate areas of retinal detachment [18].

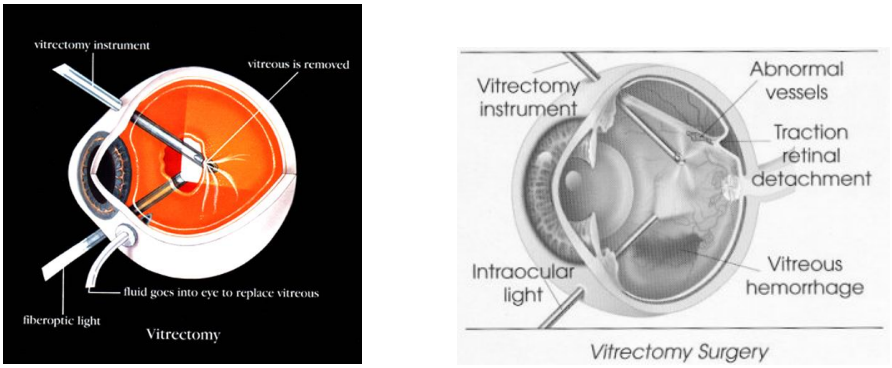

Figure 2. *(Left) Illustration of vitrectomy. Three ports into the eye for the vitreous cutter, the endoillumination probe, and the fluid cannula. The surgeon has control over the pivot of the cutter and the light source. (Right) Illustration of emergencies treated by vitrectomy. Image search keywords: "vitrectomy".*

By personal account of Dr. Joo Yong Lee, a vitrecomy surgeon from Asan Medical Center, whom we are currently in contact with, vitrectomy is difficult to perform especially because surgeons are gauging by what they can see through the patient's pupil and also because the vitreous humor is transparent. It would be beneficial to be able to see additionally through an endoscope, as well as a 3D image that can also detect the vitreous humor. Our project aims to develop a probe that simultaneously serves as a light source as well as a multi-imaging endoscope and will replace the endoillumination probe.

Currently, endoscopes ranging from 13 to 23 gauge are being used in the clinic, where the narrower 20-23 gauge probes can achieve sutureless vitrectomy [19], [20]. However, limited by their 2D viewing nature, endoscopes have been trending towards 3D imaging technology such as optical coherence tomography (OCT). OCT, due to its high resolution capabilities, would be greatly beneficial to the surgeon during a vitrectomy.

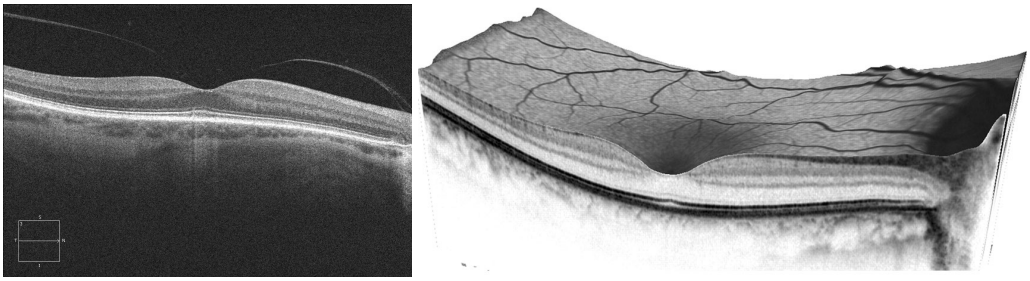

Figure 3. (Left) Example of 2D cross section OCT of retina. (Right) Example of 3D OCT imaging of retina. Image search keywords: "retina OCT"

OCT is an imaging technology that takes advantage of the infrared absorption and reflective properties of material for 3D imaging. The emission power of infrared used in the clinic is reduced to eliminate radiation damage and is thus used for imaging tissue. The contrast of the image comes from the medium's ability to reflect infrared and the imaging depth depends on the focus of the scanner in conventional OCT.

A 21-gauge OCT endoscope was developed in 2008 for the visual guidance of vitrectomy [20]. However, we believe that using solely an OCT probe will have its limitations. In addition, 21 gauge corresponds to a diameter of 0.82mm, where our goal is to achieve 25 gauge, which corresponds to a diameter of 0.51mm. In our project, we believe that we can enhance the scanning rate and the resolution of the current OCT device to enable real time, 3D imaging, as well as combine it with a white light endoscope. This will allow the surgeon to visualize a magnified view of the surgical site as well as a cross section of the underlying tissue to allow for a more efficient operation.

Method:

The technology will be based on an endoscope that has been developed in our lab; it is a miniaturized imaging probe added onto an objective lens based OCT system.

Path of OCT laser

We will use a wavelength-swept source (SSOCT-1310, Axsun) with a center wavelength of 1310nm, bandwidth of 103nm, output power of 20mW, and a sweeping speed of 50kHz for OCT, and a white light source, which we plan to purchase. The wavelength swept source will send light, which will be split by a 90/10 ratio to the sample and reference arms of an interferometry setup. In the sample arm, light from the fiber will be collimated to 2-3mm in diameter, and sent to the 10x objective lens, which will focus the light to the sample by the probe. We want the effective NA of the OCT beam to be approximately 0.1. The reflected light from the tissue sample will be coupled back to the imaging probe and delivered to the optical fiber. The reflected light from both the sample and the reference arms will then be combined at the detection arm where the interference signal will be collected and processed. Finally, the dispersion difference between the reference and sample arms will be compensated numerically by using pre-calibration data with a mirror sample.

Path of white light

We will use a white light source, which will send white light to the fiber bundle. The light from the fiber bundle will be redirected to the sample. Reflected light from the sample will be magnified by the 10x objective lens, diverted by a beam splitter, and sent to a CCD via the fiber bundle.

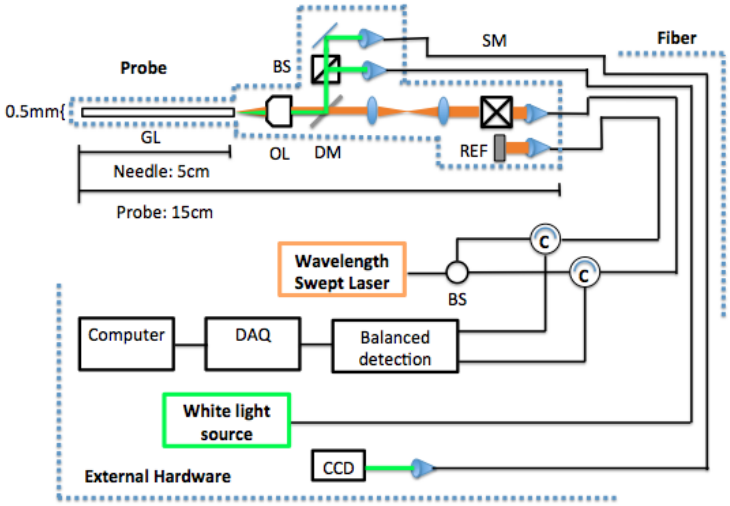

Figure 4. Proposed system schematic. 3 sections: probe, fiber, external hardware. SM: scanning mirror, DM: dichroic mirror, REF: reference arm, BS: beam splitter, OL: objective lens, C: circulator, OCT beams – orange, White light beams – green.

Detailed Plan:

1. Development of miniaturized OCT integrated with white light microscopy:

- Optical design based on endoscopic OCT and white light microscopy
- Development of wide-viewing lens based on 10x magnifying GRIN lens to obtain a field of view of 4mm and effective NA of 0.01
- Relay lenses paired with GRIN lens to compensate for insufficient length of GRIN lens
- Include dichroic mirror, which transmits OCT laser and reflects visible light in order to achieve simultaneous white light source imaging and high depth-of-focus 3D OCT imaging
- Match the difference between optical path sample and reference by adding a delay unit within the coherence length of the light
- Compensate the dispersion due to optical element
- Achieve 25 gauge probe dimension
- Utilize silicon based CMOS camera to increase sensitivity for white light imaging

2. Characterization of lateral resolution and imaging depth using 10μm diameter microsphere, followed by characterization with tissue samples

- Use Point Spread Function (PSF) and Gaussian fit to measure the lateral resolution
- Measure the system sensitivity, preferably greater than 85dB
- Imaging of ex vivo normal tissue and ex vivo affected tissue using cow eye
- Comparison of measured depth-of-focus with theoretical values
- Other animal model experiences will be conducted in Asan Medical Center

3. Optimize the design according to clinical or surgical specifications

- Handheld probe designed for flexible positioning
- Specifications: probe diameter (0.5mm-0.8mm), needle length (5cm), handle length (10cm)
- Weight: light enough to be carried by the hand for several hours without physical strain
- Create user-friendly GUI for controlling OCT and endoscope
- Consider other specifications of potential customer

4. Human clinical trials after the approval of Institutional Review Board

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Expected Effect and Application Method:

We expect to encounter two major obstacles during this project. The first is to achieve a wide field of view (4mm) relative to the diameter of the probe (0.5mm) while maintaining optimal resolution. The second is to reduce our proposed system to the dimensions of a handheld probe. Our system, utilizing technology that is commercially available, will be very bulky and heavy in size and not be suitable as a handheld device. Caltech was able to bypass these problems by developing a probe with a customized endoscopic lens that allowed them to increase the field of view while eliminating the need for a large objective lens and scanner, however, at the expense of only producing a 2D OCT image, which is simple a cross section image of tissue. This indicates to us that such technology is possible, which is why we are pursuing this challenge.

Upon the completion of this project, we will have manufactured a handheld probe, connected to a light source and data acquisition hardware via cable. The surgeon will be able to comfortably hold the probe by the handle, insert the endoscopic needle portion into the eye, and adjust the location of imaging. We will have completed a software specific to this technology, which will simultaneously display real time imaging of the combined white light endoscope and OCT probe and allow for user interfacing.

This technology may not only serve beneficial to vitrectomy, but to other surgeries and diagnostic procedures trending toward minimal invasiveness as well.