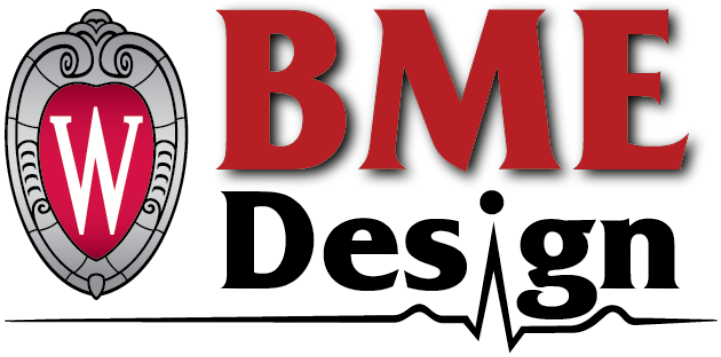

Product Design Specification

Optical Imaging of the Small Airway Mucosa

Team Members:
Yash Shah
Jade Berget
Andy Slayton
Sofia Castagnozzi
Lillian Zahn
Peter Wawrzyn

Client: Dr. Allan Brasier

Advisor: Dr. Filiz Yesilkoy

September 23, 2022

Function:
The goal of this project is to create and validate an optical frequency domain imaging (OFDI) probe for imaging in the airway of small animals. The cells lining the airway play an important role in common airway diseases and new therapeutics are being developed for treatment. A limitation in the work to develop these therapeutics is the difficulty of measuring changes over the course of an experiment. Some imaging techniques, including OFDI, are able to monitor changes in the airway; however, they are too large for small animal testing. Due to this problem, the aim of this project is to create an effective miniaturized OFDI probe for the use in animal testing.

Client requirements:

- The imaging device must be able to visualize the airway mucosa of mice in vivo.
- The device must be able to be maneuvered through a mouse airway for imaging.
- The project's budget is up to $10,000 depending on availability of already purchased resources

Design requirements:

1. Physical and Operational Characteristics

a. Performance Requirements: The imaging device must be able to image the airway mucosa of a murine test subject. The device should be able to measure up to 1 mm in depth of the airway mucosa and should have a resolution of 5 - 20 μm, which is comparable to existing OCT systems [1]. The device should not harm the mouse when sedated to allow for testing throughout a drug testing protocol.

b. Safety: The device must come with clear and concise instructions for device usage and must only be used by a trained operator with animal subjects training [2]. The device material must not cause biological harm to the mouse or the user and no sharp edges should be exposed as part of the device that could cause internal injury to the mouse subject during imaging.

c. Accuracy and Reliability: The device must have a Signal to Noise Ratio (SNR) of 80 or more, which is a baseline for imaging biological targets [3]. The imaging device must also demonstrate significant correlation ($p < 0.01$) between calculated airway wall layer areas using histology, ex-vivo, and in-vivo approaches [4].

d. Life in Service: The imaging probe should be reusable on different subjects, operating at least 10 minutes per use, averaging 2 minutes per data set with OFDI technology, [5] or 4 minutes with OCT technology [6]. The material of the probe will be sterilized by autoclaving.

e. Shelf Life: The shelf life will be dependent on quality of materials, e.g. fiber optic cable, biocompatible finish.

f. Operating Environment: The imaging probe must withstand temperatures between 20°C (68 °F) and 135°C (275 °F) for storage and sterilization conditions. The probe must also avoid corrosion from in-vivo testing and sterilization chemicals.

g. Ergonomics: The imaging probe must be made out of a material that can be used safely inside an organism with no reaction and can be sterilized. It must be able to maneuver the cartilage rings in the upper part of the trachea and measure within the airway mucosa [7].

h. Size: The probe must be able to fit inside the airway of a mouse. Its diameter must be less than 1.5mm, the diameter of a mouse trachea [8].

i. Weight: The probe must be light enough to be hand maneuvered by the same hand and weigh no more than 5.1 pounds [9].

j. Materials: Potential materials that may be included are fiber-optic cables, polycarbonate plastic, and a camera and lens. The materials will all be biocompatible and autoclavable if the design is made to be reusable.

k. Aesthetics, Appearance, and Finish: The finish must be smooth to limit physical interference of the sample. The finish must be biocompatible. The appearance and aethstetic of the device does not contribute meaningfully to its efficacy .

2. Production Characteristics:

a. Quantity: We will manufacture one final design and test it in the small airway mucosa of a small mouse.

b. Target Product Cost: The manufacturing cost may be more expensive due to the specialized style of optical imaging necessary. The total cost should be approximately $5,000-$10,000. Although

this cost is high, the total cost can be made lower based on materials already readily available to our team.

3. Miscellaneous

a. Standards and Specifications: Must avoid or minimize discomfort, distress or pain consistent with sound scientific practices [10]. Animals that are subject to prolonged discomfort or distress must be given proper sedation [10]. Animals must be humanely and safely handled, treated and transported [11].

b. Customer: The customer is asking for a device which can image the mucosa in lab mice to record the effects of trial drugs. Mice are sedated prior to imaging. Perturbation of the mucosa and other tissue by the probe would negatively impact the accuracy of the data taken. The customer would like a feature of the probe to indicate the depth of the probe in the mouse.

c. Subject-related concerns: The materials and maneuverability of the probe must ensure the mouse is unharmed and procedures follow lab animal safety protocol while using the product.

d. Competition: Hariri et. al. published a study in 2012 recording the use of OFDI on human lung imaging. The study described two methods, one of bronchoscopy airway-centered imaging and one of parenchymal imaging. A custom-built bronchoscope was used with a diameter of 0.8 - 1.7 mm. The OFDI methods were only performed on human lungs [12].

Templin et. al. published a study in 2010 that successfully used OFDI for stent healing evaluation in vevo on pigs. The study described using a Terumo-OFDI catheter on a 0.014-inch guidewire. The study successfully used OFDI on the animals 1, 3, 10, 14, and 28 days after the stents were implanted [13].

Vakoc et. al. published a study in 2006 where OFDI was successfully performed on the distal esophagus of two swine using a 4.5 cm long inflatable balloon. The study successfully acquired cross sectional imaging of the mucosal vascular network within two living swine [14].

No patents were found for a product that could successfully use OFDI in the airways of any animals smaller than pigs.

References:

[1] S. Aumann, S. Donner, J. Fischer, και F. Müller, ‘Optical Coherence Tomography (OCT): Principle and Technical Realization’, στο High Resolution Imaging in Microscopy and Ophthalmology: New Frontiers in Biomedical Optics, J. F. Bille, Επιμ. Cham: *Springer International Publishing*, 2019, σσ. 59–85.

[2] *What Investigators Need to Know Who Must Comply With the PHS Policy?*, vol. NIH Publication No. 16-OD-6009. 2016.

[3] Z. Yaqoob, J. Wu, και C. Yang, ‘Spectral domain optical coherence tomography: a better OCT imaging strategy’, *BioTechniques*, τ. 39, τχ. 6S, σσ. S6–S13, 2005.

[4] J. N. S. d’Hooghe, A. W. M. Goorsenberg, D. M. de Bruin, J. J. T. H. Roelofs, J. T. Annema, και P. I. Bonta, ‘Optical coherence tomography for identification and quantification of human airway wall layers’, *PLoS One*, τ. 12, τχ. 10, σ. e0184145, Οκτωβρίου 2017.

[5] M. J. Suter, B. J. Vakoc, P. S. Yachimski, M. Shishkov, G. Y. Lauwers, M. Mino-Kenudson, B. E. Bouma, N. S. Nishioka, and G. J. Tearney, “Comprehensive microscopy of the esophagus in human patients with optical frequency domain imaging,” *Gastrointestinal Endoscopy*, 26-Sep-2008. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0016510708018361. [Accessed: 22-Sep-2022].

[6] V. Kaul, “Optical coherence tomography for Barrett esophagus,” *Gastroenterology & hepatology*, Apr-2018. [Online]. Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6009188/. [Accessed: 22-Sep-2022].

[7] C. G. Irvin and J. H. T. Bates, “Measuring the lung function in the mouse: The challenge of Size,” *Respiratory research*, 15-May-2003. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC184039/. [Accessed: 22-Sep-2022].

[8] K. Kishimoto and M. Morimoto, “Mammalian tracheal development and reconstruction: Insights from in vivo and in vitro studies,” *Development (Cambridge, England)*, 01-Jul-2021. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8276987/#:~:text=The%20diameter%20of%20the%20mouse,different%20between%20mice%20and%20humans. [Accessed: 22-Sep-2022].

[9] C. Zingale, V. Ahlstrom, and B. Kudrick, “Human Factors Guidance for the Use of

Handheld, Portable, and Wearable Computing Devices ," *FAA human factors (ang-E25) 2005-human factors guidance for the use of handheld computing devices*, Nov-2005. [Online]. Available: https://hf.tc.faa.gov/publications/2005-human-factors-guidance-for-the-use-of-handheld/. [Accessed: 22-Sep-2022].

[10] "PHS Policy on Humane Care and Use of Laboratory Animals." *National Institutes of Health*, U.S. Department of Health and Human Services, https://olaw.nih.gov/policies-laws/phs-policy.htm#HealthResearchExtensionActof1985.

[11] "The Federal Register." *Federal Register :: Request Access*, https://www.ecfr.gov/current/title-9/chapter-I/subchapter-A/part-4.

[12] L. P. Hariri, M. B. Applegate, M. Mino-Kenudson, E. J. Mark, B. D. Medoff, A. D. Luster, B. E. Bouma, G. J. Tearney, and M. J. Suter, "Volumetric optical frequency domain imaging of pulmonary pathology with precise correlation to histopathology," *Chest*, Jan-2013. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3537541/. [Accessed: 20-Sep-2022].

[13] C. Templin, M. Meyer, M. F. Müller, V. Djonov, R. Hlushchuk, I. Dimova, S. Flueckiger, P. Kronen, M. Sidler, K. Klein, F. Nicholls, J.-R. Ghadri, K. Weber, D. Paunovic, R. Corti, S. P. Hoerstrup, T. F. Lüscher, and U. Landmesser, "Coronary optical frequency domain imaging (OFDI) for in vivo evaluation of Stent Healing: Comparison with light and electron microscopy," *European heart journal*, Jul-2010. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2903715/. [Accessed: 20-Sep-2022].

[14] B. J. Vakoc, M. Shishko, S. H. Yun, W.-Y. Oh, M. J. Suter, A. E. Desjardins, J. A. Evans, N. S. Nishioka, G. J. Tearney, and B. E. Bouma, "Comprehensive esophageal microscopy by using optical frequency–domain imaging (with video)," *Gastrointestinal Endoscopy*, 26-Mar-2007. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0016510706026691. [Accessed: 20-Sep-2022].