Awardee: Robert H. Webb, Ph.D.
Award No: DE-FG02-91ER61229

FINAL REPORT
Center of Excellence for Laser Applications in Medicine: Microscope ER61229

The Center of Excellence for Laser Applications in Medicine at the Schepens Eye Research Institute (SERI) is a Center for:

A core group of researchers who support each other and their various projects for real-time medical imaging and diagnostics in contiguous space at SERI.

Clinical collaborators who participate in the core research at SERI, MEEI and local ophthalmology practices, and at associated sites around the world.

Industrial partners who transfer our technology to commercial products that will reach clinical usage everywhere.

Students, post-doctoral associates and medical fellows who work with us and learn how to develop and how to practice real-time medical imaging and diagnostics.

Research projects within the Center are primarily independently funded, but the innovative new technologies that make us unique depend on critical support from the Center of Excellence for Laser Applications in Medicine. As we close out the Center of Excellence funding, most of the projects have become mature enough to be started on the route to commercial development that will guarantee their eventual use in clinical medicine or to availability to researchers beyond the Center. Others, more long-term and less applied as yet, are now sufficiently well covered by their other funding, though the flexibility of the Center of Excellence funding will be missed.

Projects

**Microlaser microscope:** This central project of the original Center of Excellence Grant has matured and given way to industrial efforts and collaborations outside the Center. Further development at SERI is currently restricted to support functions.

The idea here is that of an array of vertical cavity surface emitting lasers imaged on an object, which is in turn re-imaged on an array of detectors, forming a tandem scanning confocal microscope that is micro-miniaturized. This was demonstrated in a number of forms, and still waits the advent of large, matrix addressable arrays.

**Tandem Scanning Ophthalmoscope:** A first bread-board version has demonstrated optical sectioning using SLMs that are digital micro-mirrors (MEMS technology). A group of researchers around the world is getting around the manufacturer's unwillingness to help in any but consumer product development, and we are profiting by this shared expertise. This is a project that has been delayed by procurement problems, and has now outlasted its (minimal) funding. Because there seemed to be no fundamental problems with the basic idea, we carried it on without funding to a demonstration of the basic ophthalmoscope function in a real eye.
A tandem scanning microscope is a type of confocal microscope that uses a mask at an image plane to illuminate the object, and an identical mask at another optical conjugate of those planes to allow confocal detection. The mask is then moved until the whole object field is tiled. In our implementation the masks are generated by spatial light modulators (SLMs). We have found that the SLMs that we originally proposed is, indeed, the appropriate one. That makes for considerable difficulty, since the manufacturer, Texas Instruments, does not support the device for any but large consumer uses like video projectors. We, and a group of researchers world-wide are solving that problem by reverse engineering, which is working. We expect the eventual commercial TSO to be independent of this supplier, since the patent is running out and others are entering the field.

Video-rate Confocal Scanning Laser Microscope for in Vivo Imaging: This is a project of Dr. Webb’s, started at the Center of Excellence and long since launched into commercial phase with Lucid Technologies of Rochester, NY. The product is a confocal microscope of the laser scanning variety that works at high enough frame rates to image cells in living human tissue. FDA has approved it’s sale as a microscope.

This in vivo confocal microscope runs at video rates and images to about 500 μm deep in tissue. It is finding many more clinical uses than the ones originally expected of it, and is generating about 10 serious peer-reviewed papers a year, though not under Center of Excellence support any longer.

Stabilized Imaging for the Scanning Laser Ophthalmoscope: An SBIR with Physical Sciences, Inc. of Andover, MA, is in phase II, and there is excited acceptance in the ophthalmic research community, as well as interest in other areas of medical imaging. New work on the improved version is just beginning. No further Center of Excellence support will be needed, but this is one of the strong successes of the program.

The idea here is to illuminate a spot on the retina with 950 nm light, dither than spot in a known pattern, and detect changes in the reflected light to derive a feedback signal that drives the SLO raster display so that the image is stable. We have been able to add 100 video frames coherently, improving signal-to-noise ratio by a factor of 10, or reducing light dosage by a factor of 100. Features that would otherwise be unrecordable in the moving eye are now visible.

Photoreceptor optics and retinal imaging: This project of Dr. Burns uses the instrument of the Spatially Resolved Refractometer project, to understand how retinal and refractive errors interact in the eye. The existing prototype continues to give useful results, but we have converted to the new commercial model, and are finding it already useful in this work. Dr. Burns has included this in his competing renewal of his NIH grant proposal, which has been funded.

The photoreceptors of the retina have a directionality that is measured in Dr. Burns’ photoreceptor alignment reflectometer (PAR), reducing hour-long sessions to measure this Stiles-Crawford effect to a few minutes. These measurements, coupled with the Spatially Resolved Refractometer (SRR) have shown that the central point (in the eye’s pupil) at which the photoreceptors aim coincides with the part of the pupil that has least aberrations – but only in about 70% of subjects.

Multiply Scattered Light Tomography: This is one of the vertical cavity surface emitting laser (VCSEL) based imaging variants derived from the original microlaser microscope project. Drs. Elsner
and Webb an enthusiastic industrial partner, Laser Diagnostic Technologies of San Diego, CA, have a Phase II SBIR, and LDT is proceeding with a commercial instrument.

Drs. Elsner has shown that layers deep in the retina (where age-related macular degeneration starts) may be imaged in the multiply scattered light that is rejected by the confocal pinhole of the scanning laser ophthalmoscope. Then, by using VCSELs as source for both confocal and confocally rejected light, a single detector can image both views, time-domain multiplexing them at video rate. The resultant image has the virtue of being able to orient the subtle deep features by the more distinct and familiar superficial features.

**Polarization imaging:** A new project of Drs. Elsner and Burns, with partners in San Diego, CA at Laser Diagnostic Technologies, has been to develop a new technique with polarimetry to visualize different structures in the eye. A proposal to NIH is not sure of funding, but we are confident that it will eventually find support.

There have been a number of ellipsometric measures of the retina, and this is one that seems less complex than currently available ones. Based on scanning laser ophthalmoscope imaging, and using our experience with time-domain multiplexing them at video rate, we think we can map the full Mueller matrix of the retina to form a diagnostically useful image.

**Augmented Vision for Low Vision Rehabilitation:** This is a novel concept of augmented vision, based on a new method of image enhancement applied to see-through display devices. It can be used for both enhancement for central scotoma and field expansion for peripheral loss. This has very exciting early results with visually impaired patients. Drs Peli and Webb have been awarded a new BRG grant that is already taking the work forward.

Dr. Peli, an expert on head-up and virtual display devices and on low-vision rehabilitation, has developed algorithms to enhance the visual scene for visually impaired patients. He couples this with new devices to change the visual field accessible to patients by means of field-shifting (Fresnel) prisms and other optical manipulators that can be built into eyeglasses. Dr. Webb’s role is to design the ultimate optics for the devices, once the image enhancement is mature.

**Noninvasive Measurement of RPE Lipofuscin:** Lipofuscin accumulates with age in the retinal pigment epithelium, and appears to be correlated with onset of age-related macular degeneration. This project of Dr. Delori’s is building up substantial data for understanding that correlation. Dr. Delori’s work is pivotal for a Phase II SBIR with OcuMetrics, Inc. of Mt View, CA. Currently awaiting review of his grant proposal, Dr. Delori’s work to detect the A2E fluorescence in the retina is at some risk for being interrupted unless we can support him for a few months.

Dr. Delori is currently investigating the fluorescence of A2E (a fluorophore of the aging retina) and is performing experiments to define how much of the fluorescence of A2E can be detected in-vivo. A2E has been identified by biochemist and cell biologists as a potential contributor to age-related decline in retinal pigment epithelium (RPE) cell function. Detection of this fluorophore in-vivo could provide much needed information about the viability of RPE cells, and provide a tool to monitor cell health in aging and age-related macular degeneration.
The enabling technology for Dr. Delori’s work is a retinal fluorometer that can distinguish all of the contributing light from the retina and the rest of the eye, allowing measurement of the critical endogenous fluorescence from lipofuscin. Dr. Delori’s work is to correlate this measurement with other markers of age-related macular degeneration over time in an aging population. Others have taken his results and use lipofuscin fluorescence as a diagnostic in the clinic. Dr. Delori continues to work on the basic mechanism and his enabling technology for evaluating it.

**Spatially Resolved Refractometer:** The spatially resolved refractometer (SRR) is in use by the Emory Vision Correction Center in Atlanta, GA, and as well as by the group at SERI. A simpler and more efficient (in patient time) instrument designed by Drs. Webb and Burns has been working in prototype form, and three new instruments are now in use, two in the Emory Clinic and one for Dr. Burns and his collaborators at SERI. This is now fully supported by the Emory group.

The idea here is to measure the aberrations of the eye, using a null method with the patient as measurer. A spot falls on the retina, passing through selected parts of the pupil, and the patient moves the spot to a central retinal location defined by another target that he or she sees. It’s like a simple video game, and takes about 3 minutes to measure the whole eye. We use this to explore the effect of aberrations on vision and the development of vision in children. Our Emory collaborators use the SRR to guide LASIK surgery of the cornea, for better outcomes in surgical correction of vision.

**Interferometric studies of the tear film:** Dr. Doane’s optical evaluation of the health of the tear film in both dry-eye patients and contact lens wearers is finishing a Phase II SBIR with OptoVision in Boston, with a commercial instrument planned. Dr. Doane is retiring this year.

This project has been important in a clinical setting for some time. The health of the tear film is evaluated by measuring its change in thickness after blinks. A fully functioning tear film wets the cornea and flows off it smoothly, without islands of accelerated dryness or increased viscosity that leads to incomplete coverage. A dry cornea is both painful and unable to pass light properly. This interferometric measure has been very successful, and Dr. Doane (in retirement) continues to monitor the use of his instrument and copies of it in local clinics.

**Flow Cytometry:** This is a continuing collaboration with Shapiro Laboratory for innovations in flow cytometry. A commercial device using these designs is under development, but an early version is already incorporating some of the concepts. (Luminex, Austin Texas). Further innovative designs with other small companies are in the works, but funding is not necessary at present.

Dr. Webb is one of the originators of flow cytometry, and his optical designs are in use extensively. However, with the need to assess CD4 occurrence in HIV diagnosis, and with a push to record ever smaller entities (bacteria, viruses, and even DNA molecules), new technology is continually proposed. Dr. Shapiro, possibly the world’s expert and flow cytometry, uses Dr. Webb for optical design in a number of new variants on the basic flow cytometer. The task is always to deliver light to the flow chamber and assess the remitted light, discriminating against light scattered from the chamber walls or other surfaces in the light path. We have recently formulated some general principles, based on our experience in confocal microscopy.
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Seeing Machine: In collaboration with Elizabeth Goldring at MIT, Dr. Webb has made the scanning laser ophthalmoscope (SLO) available as a seeing machine for the visually impaired. Because that is not the SLO’s primary function, it is an inappropriate instrument for such a use. We have now designed an inexpensive alternative based on video projector technology, and feel that will be a useful device both as a low-vision aid and as a display device in vision research. This effort is entirely unfounded, so it has been dependent on Dr. Webb’s support through the Center of Excellence program. Funding has been requested (of NEI) for follow-on work.

The SLO works so well in part because it is a high brightness display, it uses a saturated color (the laser), and because its display is in Maxwellian view. That means that the beam entering the eye uses only a small part of the pupil, the sub-beams being substantially collimated at the pupil. With the resources of the video projector, we feel we can achieve Maxwellian view, and because there is much more light than we need, we can reach the brightness and saturation required.

Training: Students, post-doctoral and clinical fellows are an important focus of our efforts. The Center attracts an interesting mix of physicians seeking additional training in basic research that has clinical potential and basic scientists with an interest in real-time medical imaging and involving technology that may be unique in medical training. This is a function that depends on the ongoing projects, so it will essentially vanish when the program ends.

Refereed papers: The Center has produced 23 refereed papers and patents published or in press, since August 2000.


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A.4. Journal Article(s)


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