Optical microsystems for disease diagnosis: an interview with Guillermo Tearney

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Abstract. JOM Associate Editor Dr. Hui Min Leung of Harvard Medical School and Massachusetts General Hospital interviews Dr. Guillermo (Gary) Tearney, the Remondi Family Endowed MGH Research Institute Chair, Professor of Pathology at Harvard Medical School, and an Affiliated Faculty member of the Harvard-MIT Division of Health Sciences and Technology. He maintains a lab at the Wellman Center for Photomedicine at the Massachusetts General Hospital. With the use of advanced endomicroscopy technologies, Tearney's lab performs development and clinical validation of non-invasive, high-resolution optical imaging methods for human disease diagnosis. Through this interview, he described how he got into the field and how important and relevant optical microsystems are to those research projects. He also gave his thoughts on the future of the field and the grand challenges that remain to be tackled. [DOI: 10.1117/1.JOM.2.4.040401]

JOM Associate Editor Dr. Hui Min Leung, right, interviews Dr. Guillermo (Gary) Tearney. View the interview at https://doi.org/10.1117/1.JOM.2.4.040401.s1.

Hui Min Leung: So my name is Hui Min Leung and I'm here to interview Dr. Tearney, who is a professor at Harvard and Mass General Hospital. Hi, Gary. I would like you to describe your academic journey for the audience, please.

Guillermo Tearney: Sure. I guess it all started for me when I was in high school and I got really interested in light. I was really somehow fascinated in holograms and really wanted to know why and how you could get 3D pictures from a single 2D sheet of film. I also when I was that age, I also was a programmer. I learned how to program at an early age on the very first early stage personal computers.

And then I went to undergraduate in Cambridge basically as a major in applied mathematics, where I learned how to program algorithms. And I started programming a lot, because that was when the first personal computers were coming out for PCs and Macs. And I learned to program dBase and ended up getting a lot of jobs programming databases for all kinds of different companies. In that process, I met a clinician, Rob Kennett, who had an idea of starting up a company called Vanguard Imaging with the concept of basically digitizing images of pigmented skin lesions and trying to determine which ones are melanomas based on automatic image processing. This was a very early stage. There were no iPhones available at that time and digital cameras were not really readily available. Computers were still very young. Personal computers were

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very new. So it involved a whole lot of technological development to get the first digital images and to develop programming algorithms and implement them. So we could automatically determine the so called A, B, C, D, and E parameters that could be automatically computed to provide a risk of a pigmented lesion being a melanoma. In that process, I met Rox Anderson, who is now the director of the Wellman Center. And Rox essentially recruited me to come to Wellman. And I came to Wellman and started doing research on a wide variety of topics. One of them was Anderson localization and polarization, light scattering of spherical particles. And I learned a lot about the optical properties of tissue. At that point, Rox encouraged me to get my PhD. And I had already just started medical school. So I started my MD PhD program and I got my PhD in the laboratory of Jim Fujimoto at MIT. At that time, it was 1992 is when right after OCT had been invented. The major thrust behind OCT or optical coherence tomography was at that time looking and seeing whether or not you could look at retinal pathologies. And my thesis in Jim's lab was to see what other areas of the body could OCT potentially be applied to for in vivo. And so I worked in Jim's lab for about four to five years. I was a graduate student and I worked very closely with Brett Bouma, who was a postdoc in Jim's lab at the time. And we developed the fastest OCT imaging systems to date to sort of deal with motion artifacts that occur when you're imaging inside the body of living people. We shifted the wavelength to longer wavelengths so that we could penetrate deeper into scattering tissues. And we developed the first catheter that could be put inside the body to get OCT images. And then after my PhD, I finished off my MD and became a pathologist, which made sense because my work up until then had really been about looking at microscopy in living people. And it made sense for me to understand how microscopic diagnoses were made in the standard of care. So I became a pathologist, did my residency at Mass General. And then in 2001, I started a joint lab with Brett where we were translating predominantly OCT but also other forms of optical microscopy clinically. And being at the hospital campus was a great place to do that, being at Wellman Center and at Mass General. And we subsequently have done lots of first-in-human studies. And now I have a fairly large lab developing all kinds of in vivo optical microscopy devices and testing them out in patients.

Leung: Yeah, it's really interesting. If you can speak more about the work of the Tearney Lab. What kind of optical microsystems you use and the endoscopy techniques that you use in your lab.

Tearney: Yeah. So in my lab, our goal is to see every cell in the body of living human patients. And so we've worked on or developed a whole bunch of different technologies that image at the microscopic level in living people. Some of them are really fast. So we can image entire organs at the microscopic level. Others have very, very high resolution. So we can see even subcellular structures like organelles.

And we used this whole panoply of technologies in a variety of different devices to look at particular applications inside the body. For example, we developed coronary catheters that go inside the arteries that supply blood to your heart, that are able of looking at the structure of the coronary artery wall with incredible detail. And this is now being used clinically. We've also developed enhancements to that where we've looked at OCT microstructure and also other imaging technologies like fluorescence or spectroscopy that can be implemented in the same catheter to provide complementary information. We've also developed a lot of devices for the GI tract. We've developed catheters that go into endoscopes, balloons that can image the entire esophagus, for example. And most recently, tethered capsules that are little pills on a tether where the tether contains the optical fiber. And the patient swallows them and they passively go down throughout the GI tract, imaging the GI tract in three dimensions. We've also developed probes for the lung, probes that go into the nose that image at the cellular level. We're developing devices that go into the ear. We've done work in the gynecological and urinary tract. So we've tried to work in most areas of the body doing some skin work. But I think our major areas have been predominantly cardiovascular and GI. And we're constantly pushing the resolution, pushing the imaging capabilities to address specific disease states. I think one of the real strengths of our lab is that we are a very multidisciplinary lab. We have lots of engineers and physicists. But we also have a very strong clinical regulatory team with nurses, physicians, clinical regulatory scientists who really push our technologies along the translational pathway into patients. We

have many, many clinical studies ongoing at any given point in time. And something we're really proud of is how we can bring our technologies from the bench to the bedside and commercialize them and ultimately have them impact patients' lives.

Leung: That's really impressive. And I'm interested to know within such a wide ranging research that you've covered so far, how do you identify the unmet clinical needs and how do you push forward so that you can better impact the biomedical field in health care?
Tearney: Yeah, I think that unmet clinical needs is the most important question that we all have to address. And I like to think that most of our projects start off with the clinical need, not the technology.

I have an MD and I have some experience from being a physician. But also we have the ability to tap into hundreds if not thousands of really incredible physicians at Mass General Hospital and also around the country and the world who bring problems to our attention, who ask us questions about whether or not our technology can be used to address a certain condition. And we research those problems not just whether or not they exist, but whether or not the solutions that we might be able to offer with our imaging technology really meet the unmet need. And I think one of the most important things is a lot of time is put in up front to make sure that we're working on the right problem and that our solution is going to really meet all the requirements that are needed to solve that problem. And that's before we even get started. So it's an important part of our process to identify those problems and utilize the knowledge that we have in terms of the medical environment, in terms of the medical health care system, in terms of patient needs, physician needs, and come up with the right solution.

Leung: Yeah. And also you mentioned looking at every living cell in the body is important for your research. And can you describe what are the unique strengths of the most advanced micro optics that are relevant for your biomedical research? And how do you exploit them in your research?
Tearney: Yeah. I mean, I think micro optics are a really important component of our research. As I've described, most of our work involves putting tiny microscopes inside the body. And so what we have to be able to do is make the optics, that's the critical component of those microscopes. And we have a variety of different technologies for creating these micro optics. We have machines that make lenses. We have two photon polymerization 3D printers at our disposal and just a lot of creativity about how to put these things together. I think one of the challenges as we get smaller and smaller is actually there comes a size where it's very difficult for human hands to actually fabricate a device. And we're pretty much at that scale with many of our devices. And I think that's one place where the two photon polymerization really can play a major role in allowing us to make even smaller optics that would be difficult to make by hand.

Leung: So how do you think, what are your thoughts on the field of optical endoscopy? And how do you think the field might evolve in the future?
Tearney: Yeah. I think optical endomicroscopy, which is really the area that I work in, is an interesting field. I think it's had some successes and it's also had some failures. And I think the successes occur because you're imaging in a system where there really is no other answer. But when you're trying to completely replace the standard of care, the bar is quite high to be able to come in with a new technology that everybody is going to adopt. And there's a learning curve. There's cultural shifts that need to happen for some of these technologies to be adopted. And also honestly, I think the technology still needs to improve. If I look at OCT or even confocal microscopy in the GI tract as an example, they're very good and they can accurately diagnose disease when people are well trained. But they're still not as good. The images aren't as good as conventional histopathology, and there are lots of pieces of information that you can't get from those images, such as what genetic mutations are there, for example.

So there still is a big gap between where we are with our optical endomicroscopy technology and the kinds of information that you can grab from just conventional biopsy. So in terms of technology development, I really do think we need to close that gap significantly before clinicians will be utilizing this technology on a wide scale.

Leung: So other than the footprint needs to be smaller, the resolution is higher, what are the major challenges?
Tearney: Well, I think one of the biggest challenges is contrast. I think the resolution probably is there with some of the more recent confocal and OCT technologies. But the contrast isn't. So the contrast that we have to work with in many of our devices is natural contrast. So the differences in scattering or in tissue. There is a possibility, of course, to provide a exogenous contrast, which may be viable in certain scenarios. But if you're using natural contrast, it's tricky. And I think that some of the interesting nonlinear microscopy technologies I think can provide better contrast. I think those kinds of technologies are really exciting for the future for that reason.

Leung: How about in general biomedical imaging field in general? What are the grand challenges that needs to be tackled by the field in your opinion?
Tearney: Well, in my area where we're doing in vivo microscopy, it's exactly what I just mentioned. We need improved contrast and improved resolution. We need clearer images in order to really compete with biopsy and histopathology in a reasonable way. Another big problem which I think some of our technologies have is when you're imaging very large areas, you end up with too much information to be able to process as a human during the time of the procedure and make an interventional decision. And so I think the real advancement in AI technologies for parsing through huge amounts of data and providing clinicians with real time or near real time feedback that they can intervene on is a really critical aspect in the future of many of these devices, especially the ones that image large tissue areas during a procedure.

I think cost, of course, is a huge issue. The bar is very high when your instrument costs over $100,000, the bar for adoption. And getting costs lower increases the number of potential applications that you can have and also lowers the bar for entry for many clinicians to utilize this technology. So I think lowering costs is another really important issue with many of the microscopy technologies that we're developing.

Leung: Yeah. And maybe AI can also help in the interpretation of large data sets that can work together with physicians in those decisions.
Tearney: Yeah, definitely AI is critical for large data sets. Because I think the real win here is that we can intervene better when we can see better. And I think I believe that and I think many clinicians believe that as well. But in order for that to happen, we have to allow those decisions to be made nearly instantaneously. And the microscopic images that we grab of entire organs is just too much for any person to be able to parse through during a realistic procedure time. So computer aided diagnosis is super important in our field moving forward, especially when it comes to these large data sets.

Leung: Yeah. Thank you so much for sharing your thoughts. Yeah, thank you for spending time to share your experience with the JOM audience too. And I wish you good luck.
Tearney: Thank you very much.