

Science AMA Series: We are researchers at Johns Hopkins. We have just developed a new kind of noninvasive probe that visualize living cells in real time and we are here today to talk about it. AMA!

HopkinsMedicineAMA<sup>1</sup>and/ScienceAMAs<sup>1</sup>

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### Abstract

Hi Reddit, we are Xingde Li (<https://www.hopkinsmedicine.org/profiles/results/directory/profile/0800034/xingde-li>), professor of Biomedical Engineering and Wenxuan Liang, a postdoctoral fellow at Johns Hopkins Medicine majoring in biophotonics. Our lab works to improve endomicroscopy in the hopes of someday diminishing our dependencies on biopsies. We have recently developed two new endoscopic probes that have a potential to significantly improve imaging diagnostics. Our first probe uses the same basics from the two-photon microscope but in a much smaller footprint. Our prototype probe, 2mm in diameter, takes advantage of the cell's own ability to glow and eliminates the need for traditional fluorophores – usually harmful to the human body. This allow us to directly visualize fine structural changes and monitor cell activity in vivo and in real time at histology level but without the need for tissue removal. (<https://www.nature.com/articles/lisa201782>) Our second probe is even smaller (approximately 500  $\mu\text{m}$  in diameter) but offers us about four times higher resolution than other currently used devices. The small probe size eases the delivery of endoscope to small areas of the body. This can greatly reduce patient's discomfort during the endoscopy procedure while also providing a high resolution and clear visualization of tissue microstructures. This is very important for detecting disease at early stages when tissue microstructural changes are subtle and the disease is still at a manageable stage. (<https://www.nature.com/articles/s41467-017-01494-4> ) We will be back at 1pm ET today to answer your questions.

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How much did your laser cost? The one my girlfriend uses on the 2 photon rig she built costs \$250K, so she would be intrested in a cheaper alternative for her next one.

[sock2014](#)

The commercial laser does cost \$250K, but we have a home-build version that costs a quarter of that. We hope to dramatically reduce the price if industry is interested. However, ours is not commercially available yet.

Hold out hope though! The price of the commercial laser has been dropping dramatically because of improved technology and higher demands. Mass production should drop the price.

What imaging depths are possible with these devices? How long does an acquisition take? How does that compare to current endoscopic techniques?

[shiruken](#)

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With the two photon probe, we can image at depths of about 200 microns, which is similar to the benchtop microscope. We can gather images at about 3 frames/second. We are currently working to improve imaging speed and depths. Ultimately, the imaging depth is limited by the fundamental physics of light transmission.

The closest technology to our two-photon endomicroscope that is clinically available is the confocal endomicroscope. Our imaging depth is twice as much as the confocal and does not rely on dyes to gather our images.

With our OCT probe, we can see down to about 3 millimeter and we can see a larger area. Our tech can see below the surface while the one used currently in clinical practice cannot.

Would you please discuss the state-of-the art of micro injection and how this technology could interact? I ask from a plant breeder and basic science perspective where the ability to perform microinjections of a CRISPR/Cas9 solution or even just a stimulating compound would facilitate studies in non-model plants (Cells are 10-100um in diameter).

[NolanBentley](#)

I'm not an expert in microinjection. It would be interesting to see if our imaging technology could be applied to see where the compounds go in the plant after receiving a microinjection.

Multi-photon microscopy is highly dependent upon the quality of the objective. Did you encounter any difficulties while working with the miniaturized optics found in endoscopes? If so, how effectively were they overcome?

[shiruken](#)

This is another excellent question! Indeed, this was a huge challenge. The benchtop scope relies on a high-quality multi-element objective, which is very expensive.

About 10 years ago, we fabricated a miniature version of this objective, but it cost \$25000 just for one piece. Clearly that's not translational and far too expensive to be disposable, which was our aim.

Recently, we found a new way to do it that is about 100X cheaper! If industry is interested, mass production will make this even more affordable. The key was developing our diffractive microoptics. We can have a diffractive lens built-into our micro objective to correct aberrations in our images and allow us to get high quality imagery. These can also be mass produced, making it much less expensive than our previous efforts.

How does your imaging technology compare to current endoscopy techniques? Have you studied its direct impact on patient diagnostics and/or discovery and identification of disease?

[adenovato](#)

The current clinical endoscope only sees the surface of the tissue, acting like a magnifying glass. Our endoscope aims to reach the cellular or subcellular level while also gathering metabolic data - all without requiring any contrast agents.

The tech is at the initial stage. We still need to do more studies in animal models before addressing our clinical impact in humans and compare it to the current clinical technology.

In the end, our tech might not replace anything, but will meet the needs not addressed by the currently available clinical technology.

The current scope can see the surface over a large area, giving us a high-level picture. Ours can see a small area in high detail. We wish to interface with the current endoscope to investigate suspicious areas in more details.

You say the second probe is approximately 500  $\mu\text{m}$  in diameter. Just how wide is that? Can you compare that to something?

How wide is a normal probe?

[sciencereader3455](#)

We just measured and 500 $\mu\text{m}$  it's about 5-6 pieces of copy paper! (See our video on Facebook!<https://www.facebook.com/JHM.Fundamentals/videos/2098038750467873/>)

There are 2 types of OCT probes used in clinics today. One that is typically used for the cardiovascular system is about 920 microns in diameter. Most of the probes are about 1300 microns.

We are also working on a completely different wavelength than existing probes (800nm) to get high optical performance. We were able to have a very small probe and achieve high performance this way.

Wait... our cells glow on their own? I did not know that! How bright do they glow and did you know that would be enough light before you made the probe or did you discover that by chance?

[scienceaccount103040](#)

It has been known for many years that our cells fluorescence and we wanted to take advantage of this with our technology.

There are quite a few molecules, NADH and FADH, the molecules we use when our cells convert sugar to ATP in cell respiration, that fluoresce. There are a few other proteins that fluoresce as well - collagen, keratin and elastin.

Compared to chemical compounds used to label tissues in the lab, our cells aren't that bright, which was tremendously challenging for us. We had to spend a lot of time and effort to pick up the weak signal. However, we didn't want to use these compounds because they can be harmful to the body - most have not been evaluated by the FDA. If someday there are some compounds that are proven safe in the body and are tissue specific, that would make our work 100x easier.

However, fluorescence and glowing are slightly different. Fluorescence, is when a material absorbs energy from light at a certain wavelength, which excites it's electrons. The light we see from fluorescence comes when that excitation energy is released and is released as light.

Why is this smaller probe more beneficial? How does it lessen the need for biopsies?

[sciencereader3455](#)

The size is important because we want to go inside small spaces in the body, like the small airways of the lung and cardiovascular vessels, without injuring them.

As for biopsies, they can be extremely invasive. One challenge in biopsy is to see where to take the

tissue out and a lot of the time the removals cannot be made with pinpoint precision and we take an educated guess of what cells may be affected by disease. With this low information, you sometimes have to take a lot of biopsies. For example, you may need to take 40 samples out from the GI tract, but the total sampled area can be less than 3% of the organ, so we cannot know what abnormalities may have been missed. We hope our technology will make it so that you won't have to take the tissue out and that you can look at multiple spots very quickly

There are also certain areas you don't want to biopsy, like the cardiovascular system and nerves. With non invasive technologies, you won't need to worry about endangering the patient by removing tissue.

in vivo and in real time at histology level but without the need for tissue removal.

So this is a big deal I take it. No more biopsies? What are the limitations of the probe? What can't it do that a biopsy can?

[scienceaccount103040](#)

It is a big deal! It is a dream for many researchers in our field.

With our technology, we'd still like to gain some specificity and some more confidence in diagnosing cancer vs. non-cancer, for instance.

Also, our imaging speed and field of view are not where we'd like them. We'd like to take images more quickly and the area we can cover is still small, about 150 microns across. However, we are constantly improving these aspects in our lab.

Another challenge is how to make the probe even smaller and even more flexible. But as a biomedical engineer, we never say never. As far as the physics and engineering permit, anything is possible.

Biopsy does still hold some advantages over our probes. Outside of the body, you can do molecular tests, like immunostaining.