

# Pushing for a new paradigm in disease management

**Netzahualcóyotl Arroyo Currás is an Assistant Professor of Pharmacology and Molecular Sciences at Johns Hopkins University School of Medicine. Applying his background in electrochemistry to the field of biological sensors, he develops aptamer-based point-of-care assays and wearable sensors for improved disease management.**

**We spoke to him about transferring this platform to the clinic and why he works in the field.**

***Could you tell us a bit about your career and how you came to work with aptamers?***

My background is in electrochemical research, the connection between electricity and matter. As my career developed, I chose to explore more about biology and biophysics, so I pursued a post-doctoral position with Professor Kevin Plaxco at the University of California, San Diego. That was how I ended up working with aptamers in the first place; I was looking at how aptamers could be applied for in vivo sensing. Through this work, I developed relationships with different companies and research faculties. A common issue in everything that we were trying to achieve was that we needed a new aptamer, or a different aptamer or a better aptamer



Even though DNA technology, in general, is very well developed, it is not that simple to isolate good aptamers.

***Why do you work with aptamers?***

The aptamers we work with are specifically selected to perform in our platform with each biomarker of interest. Aptamers have a unique property in that they can be tailored to undergo binding-induced conformational changes, also called structural switching, and they can do this reversibly.

Using a system where the binders can bind and dissociate reversibly means that the receptors (the aptamers) are being spontaneously regenerated. The timescales for the aptamer refolding process can take anywhere from microseconds to hundreds of milliseconds, a time range that is much faster than any practical

measurement you would take in a patient. This gives us the ability to continuously interrogate the system using devices like wearable sensors. You don't have that capability with antibodies; thus, aptamers offer a unique property that antibodies currently cannot match. Because of the folding dynamics and the structural changes in aptamers, they afford real-time continuous sensing in complex biological fluids in a way that antibodies cannot.

We shouldn't think about aptamers vs antibodies. It is not a case of one or the other. Thinking of only one kind of affinity reagent limits your creativity and scope. You have to think outside the box, and that is what we're trying to do. We're trying to think outside the box and eliminate the problems we have, and for our problems, aptamers offer the right solution.

The sensors we develop are implanted into the body. They remove the need to take a patient sample, such as a blood sample in the clinic, send it away for sample processing and further analysis using tests such as immunoassays. We can place the sensors directly in vivo and then interrogate the environment inside the patient continuously for hours at a time, receiving real-time data on different physiological processes. This is useful for monitoring drug pharmacokinetics at an individual patient level, allowing us to tailor their treatment regime to their particular needs and the way their body reacts. The molecular targets being measured can be changed by simply switching the aptamer on the sensor.

### ***How does the biosensor that your lab is developing differ from other currently available biosensing platforms?***

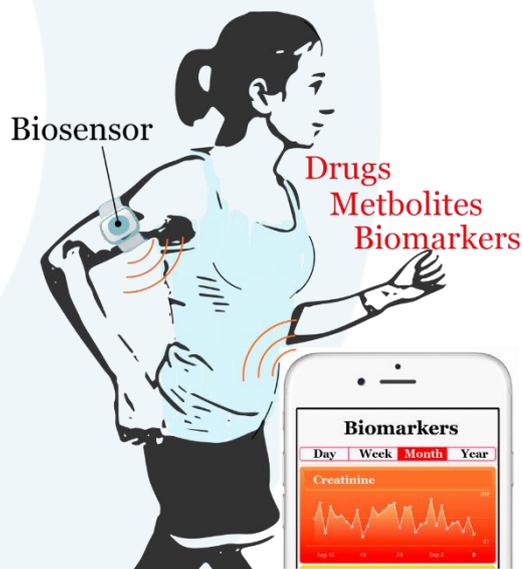
We have developed a tool that, for the first time, enables the continuous measurement of biomarkers within the body with very high specificity. As a biomedical research tool, both in humans and animals, it is unprecedented.

It could be applied to patients to monitor drug dosing, to understand metabolic changes, or to track biomarker concentrations all in real-time. Why should you have to come to a lab for a blood

draw if we can remotely measure blood biomarker and drug concentrations to understand disease risk and susceptibility?

We are collaboratively developing microneedle arrays for use as wearable sensors that offer a non-invasive or minimally invasive assessment. These consist of a small patch that is placed under the skin in a completely pain-free manner. The microneedles penetrate the interstitial compartment allowing real-time monitoring of the biomarker of interest. We aim to get this into the clinic, but we are working on the research aspects of it right now.

Another critical application of our technology is point-of-need measurement. While this application does not make use of the reversible structural switching of the aptamers, it does depend on the ability to measure accurately in whole blood samples without having to process the sample further to plasma or serum or dilute it extensively for an immunoassay.

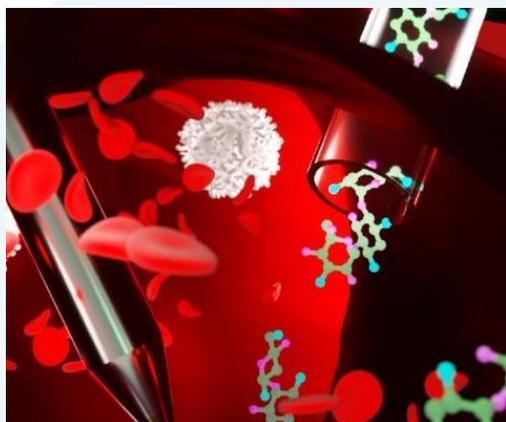


*Real time assessment of health status could bring a new paradigm in disease management.*

We have a blind clinical validation study currently underway to assess the performance of our platform relative to the standard immunoassays and LC-MS that are currently used. I know other groups are pursuing this point-of-care style assay at other hospitals across the world. Should the results of our trial be as positive as expected, then

we want to try to take the platform to the clinic and apply it to critical medical problems.

My lab is fully devoted to the translation of our platform, and we are pushing hard to get to the clinic.



*The team's in vivo sensing technology uses aptamers to allow continuous monitoring of specific biomarkers for truly personalized medicine.*

Our application is so unique, and in my opinion, so important because few platforms in the world achieve real-time continuous sensing of specific biomarkers based on affinity. The only other major competing technology is continuous glucose monitoring, which has been in the market for a long time. Continuous glucose monitors rely on enzymatic activity, meaning that the technology is not generalizable, as you need a specific enzyme for every biomarker that you want to study. That is just not practical as most of those enzymes do not exist. Instead, we are using affinity and binding in a way that can be translated to a greater variety of molecular markers.

***Considering the long term in vivo measurements that your sensors offer do you need to consider the stability of the aptamers when engineering your sensors?***

DNA is surprisingly stable in serum. The serum concentration and activity of nucleases are very low, and if you add DNA, it lasts a remarkably long time in serum.

My group has published a paper showing that

nucleases do not drive the signaling decay in our sensor – the timescales for the processes did not match. Nucleases take a much longer time to degrade DNA than the signal decay we were seeing. We found that the chemistry we were using to form the devices was driving the signal decay, not the DNA aptamers. Since discovering this, we've devoted intense research to changing the chemistries that we use so that we can eliminate this problem.

***Different aptamer modifications can be engineered to increase stability of specificity. Have you explored these within your platform?***

The available DNA modifications, such as changing the phosphate backbone, locking the sugars, or adding fluorine, may not work on our platform because they change the conformational dynamics of the DNA, unless the aptamers were purposefully selected from libraries containing such modifications. These changes would likely affect the binding and refolding of the aptamer, slowing down their on/off binding dynamics.

SomaLogic has successfully developed a platform using modified aptamers that are specifically designed to compete with antibodies in a sandwich-type assay. But this doesn't mean they are the best chemistry for the platform we are developing.

There's not just one way of doing things, but many. Perhaps sandwich assays are the biggest market right now, but many new markets and novel methods are emerging that will be equally as attractive in the near future, and these often require alternative performance characteristics.

***What sort of impact do you think your sensors could have on healthcare?***

I don't want to pigeonhole our work into diagnostics or therapeutic drug monitoring, I want to think bigger about disease management, about real-time assessment of health status.

If we take the example of anti-infectives, all

the current technologies monitor the drug molecule. What if we could analyze the drug and monitor pharmacodynamics examining the biomarkers at the same time, and couple the two? I think that's something pretty unique. To be able to monitor biomarkers in real-time with straightforward methods could be a very powerful tool for disease management.

From something as small as taking a standard blood panel, we could perform the analysis in real-time without having to draw blood and wait days for the results. My wife recently got a standard blood analysis, and everything looked normal, but a few markers were near the limits of 'normal' ranges. The doctor's first reaction was, 'I think the laboratory may have made a mistake. Let's do it again.' Now imagine a technology that can monitor the same thing in real-time with hundreds of data points. There is no mistake by a user or robot, and the data is there to act upon immediately.

I think it's going to transform how we understand and diagnose disease. It will change the paradigm we use to look at this problem.

Even though the technology can carry out instantaneous real-time analysis, it will be faster to prove the platform's performance as a diagnostic. In the first instance, we will likely go to the clinic with the analysis of single-point measurements of the same sorts of biomarkers that we currently monitor in a routine blood sample. This will probably involve the current workflow of taking a sample from the patient and monitoring it on the device, to prove the technology. However, using our system for analysis would provide rapid point-of-care results for immediate treatment.

The biggest challenge to the successful translation of any biomedical technology is, in fact, adoption. That's why it's important to find an application for which an answer is not currently available because it lowers the barrier for entry.

## ***How long will it be before we start to see your devices in clinic?***

The problem with clinical translation is that you cannot translate a general platform to the clinic. I can't go to the doctors in a hospital and say, 'We can use this system to monitor anything that you want'. You have to approach clinicians with a specific solution to something they cannot currently do.

A very intensive part of my job is talking to clinicians to find the right niche to tackle first. Getting that right will allow us to penetrate the medical market and gain interest from clinicians.

I think the clinical demonstration of the platform at a pilot level will occur over the next two years. You won't see the platform commercialized, but you will likely see these assays being used in research about three years from now. So, it is happening.

The first product we are hoping to bring to the clinic will be the point-of-care device currently under clinical validation. Depending on the results from that pilot study, we will determine the next steps, such as what it is that makes our product truly unique. We have ideas, but it will ultimately depend on the outcome of those pilot clinical studies.

If I can be slightly optimistic here, I think you will see our devices in the clinic within the next ten years.

## ***Your plans for your platform straddle both academia and industry. Where do you see yourself fitting within these sectors?***

I have started companies before, but I didn't enjoy the process. I really enjoy working with my students and trainees, helping them develop their careers while at the same time providing solutions to the world.

Through earlier experiences in my career working on the more industrial side of science, I realized that what I enjoy is the science and tech transfer. We're currently working with three different

companies that are helping us commercialize our technology. To me, that is much more enjoyable. I don't have the specific phenotype needed to lead a venture company, but I can still be deeply involved in the R&D in that world. I think these kinds of collaborations benefit both worlds.

It comes down to what you need in life. As a scientist, I dream about being able to help people. Just like the glucose biosensor helped so many diabetics in the world, what if we could make an advance and change one person's life or many people's life in a significant way? My greed for service to society overcomes my greed for money.

### ***What do you envision as the future for aptamers?***

Aptamers are here to stay. There are therapeutics, diagnostics and then research and a number of other fields that can all be addressed with aptamer technology. There are many technological milestones that need to be met, but I think we are already seeing aptamers becoming more pervasive across the board, just like antibodies did. I don't anticipate that they will replace the use of antibodies, but there are

certain applications, maybe niche applications, maybe non-niche applications, I don't think we know yet, but there are definitely areas where they excel.

I think eventually we will reach a point where we can design aptamers de novo in a computer program and effectively predict their behavior, in a manner analogous to the latest drug discovery processes using AI within the pharmaceutical sector. We're definitely going in this direction, but it is a big milestone with lots of work needed before we get there.

As much as we love antibodies, they come with many disadvantages and can be quite difficult to work with. Think about flying antibodies into sub-Saharan Africa, where you might not have access to a -20°C freezer? It's not possible. If you start thinking outside of the comfort zone of a rich country, about applications in low-income regions of the world we need alternative technologies that can help us address needs that cannot be met with the current technologies, or that can address the same needs at a lower cost. I think that is where they applications of aptamers will emerge.

Find out more at [aptamergroup.com](https://www.aptamergroup.com)