The development of the Zepto capsulotomy device is more than a little unconventional: ten years ago, two newcomers to the field (us), with very little funding, no experience of medical device development, and no track record in ophthalmology, decide to work together to create a new capsulotomy device. From that background alone, you’d be forgiven for thinking it was a long shot. But since that lightbulb moment, we’ve come a long way – the Zepto capsulotomy device received a CE mark in 2015, and our work was presented at the 2015 Ophthalmology Innovation Summits in San Diego and Las Vegas, and the 2015 Ophthalmology Futures Forum in Barcelona. And it all began with micromechanical knives…

Gizmos and glaucoma

Before we met, Chris had worked at IBM for 10 years, designing hard disc drives, before returning to school to undertake a PhD in material science at the University of California, Berkeley. The research was fascinating; it focused on microelectromechanical systems (MEMS), which are made on silicon wafers using integrated circuit processes to create micromechanical devices. Because working for such a large company no longer appealed to Chris, after graduating, he started his own sole proprietorship creating nifty little gizmos, such as microknives, for the local professors. David, who was using microknives to perform surgery on individual nerve cells growing in petri dishes, became a customer. It wasn’t long after meeting that we decided we wanted to work together to develop a practical medical device.
At first we focused on glaucoma – our idea was to create a device that would enter Schlemm’s canal and cut the wall to enter the trabecular meshwork, creating another outflow pathway. But although we worked on the idea for some time, we didn’t meet with much success. We were relative newcomers to the field, and at the time a lot of MIGS companies were being launched and netting funding, and we were much further ahead than us. In 2008, venture capital funding was also very scarce, and we had no luck getting our idea funded. So, we were left scratching our heads. But if we had to keep it simple. In some ways this became an advantage, as it forced us to be much more creative than we might have otherwise been.

One of our first tasks was to look at the literature, to see what methods had been tried in the past – one method which is in some ways similar to ours is in the Fugo Blade. But this device involves using a probe tip that has to be moved in a circular fashion, it makes success very dependent on the surgeon’s skill. We aimed to design a device that wasn’t limited by this issue.

Initially we tried mechanical methods, in the same vein as the microknives we’d both worked with before, but it soon became clear that this wouldn’t work. Our next idea was to use a tiny micro spot welder that was made from gold wire, just 100 µm in diameter. We tried it with a lens from a rabbit eye, held it up to the lens ran a current through the fine gold wire by discharging a 20 µF capacitor through it. It made a cut, so we knew it would work. Having worked in a microenvironment before, we knew that we had to use a short pulse to avoid collateral damage to neighboring tissue, so the energy density was important, and had to be highly localized in both space and time. There also had to be a force pushing the membrane against the electrical cutting element.

When it came to force, we took a cue from squid – their use of suction cups to create a complete force circuit and grip onto things is both elegant and uncomplicated. We wanted a similar suction cup gripping the surface of the lens, pulling it into the cutting element, so that the capsule is under mechanical tension exactly on the circle you want to cut. This means there’s no force going anywhere else in the eye, and you’re not pulling the zonules, or putting other area under strain (Figure 1) – the force circuit is entirely contained within the suction cup and the front of the lens. We built some prototypes to test our idea, and they worked very well! We needed some images to demonstrate what our device could do, so Chris went and paid a fee to the University of Berkley Electron Microscopy Imaging Center to take some scanning electron microscope images to demonstrate what our device could do.

Cephalopod capsulotomy

So despite the advent of laser capsulotomy, we kept working on our device. With no money for fancy lasers or expensive equipment, we knew we had to keep it simple. In some ways this became an advantage, as it forced us to be much more creative than we might have otherwise been.

Funding firsts

Developing and obtaining proof-of-concept for this idea was critical – if we had tried to approach institutional or venture capital funding before that point, it would probably have been unsuccessful (this was the time of all the hype around femtosecond lasers). So this was a project that required a lot of initial investment and hard work from just the two of us. And when it came to finally obtaining some funding, we were in luck. We developed our proof-of-concept using rabbit eyes, primarily because they were cheap and convenient to use.

**Zepto – How it Works**

The Zepto capsulotomy tip can collapse to enter the primary corneal incision (A–D), then re-expand to a circle within the anterior chamber (E). Once aligned over the visual axis (F), suction is used to oppose the radial ring against the capsule. Using a multiphase algorithm, precision-pulse technology is used to cause rapid phase transition of the water molecules underneath the ring, cleaving the capsule membrane and simultaneously creating all 360° of the capsulotomy (G).

The tip can then be collapsed and removed (H) along with the excised tissue (I–J). To view the video, go to top.txp.to/issues/0215/301.
But it’s also known that the rabbit capsule is similar to that of an infant, in that it’s very elastic. It was this initial focus on pediatric applications that helped us to secure our first grant. The National Eye Institute (NEI) in the US is particularly interested in developing ophthalmic devices proven to work in pediatric patients, because of the lack of devices commercially available that are suitable for this patient group. The result? A lot of children consigned to having instruments used in their eyes that were developed for adults – not an ideal situation.

This inspired us to approach them with our idea for a device that would work particularly well for pediatric capsulotomies. When we showed them our data, they were interested, and we netted our first grant support, helping launch us onto a faster trajectory. Ultimately, we were able to get a whole series of Small Business Innovation Research (SBIR) grants awarded to our company, and several other government grants too. This allowed us to proceed with our project without needing institutional or venture capital investors.

**From proof to prototype**

Having some funding accelerated development, and we were able to move from a device that demonstrated our cutting method, to a working prototype of Zepto that could be used surgically (see sidebar “Zepto – How it Works”). It satisfied all of our initial design goals: a small incision device that could computationally (dilated or centering the visual axis). This was a completely serendipitous discovery.

“Once we had our prototype, we realized that the thin-walled suction cup we were using essentially disappears when you put it into the eye. You could actually use the device for visual centration during the procedure.”

**Bringing in the business experts**

Now that we had our surgical prototype, we knew we needed to find experienced management to help us. We simply didn’t have the know-how to gain regulatory approval – if we’d tried to do it ourselves, we would likely have been foundering and wasting a lot of money making avoidable mistakes. So we started networking,

making contact with people who could potentially come on board. John Hendrick was one of the names that came up, and we made an appointment to see him. John told us he was interested, but didn’t yet know if he would be available to work with our company, Mynosys, as he was waiting for the results of a clinical trial at the company he was working with at the time. He told us to call in four months and he’d have an answer, and we did. Luckily for us, he was free, and realized the potential of Zepto (see “Going for Gold”).

Having John and his team to help us navigate regulatory approval has been fantastic – John himself was previously Vice President of Operations at Allergan Medical Optics, and actually led the team that developed the first foldable silicone IOL, so he’s very familiar with cataract surgery. In fact he told us that back in those days he led a team that tried to develop a capsulotomy device, but it didn’t work out. The idea stayed with him, and when he saw the videos that Chris and I had brought to our first meeting, the light bulb came on in his head and he realized that – aha! – this might actually be it, what he had been trying to do so many years ago, and what other people had been trying to do in the years since.

So now we’re transitioning our product towards production, and we’ve very lucky to have John’s expertise – he is a true master of the art of contract manufacturing. He understands the margins and timeframes, and has an amazing network of contacts to draw on. He knows whom to go and who to see, and these are things it could have taken us a very long time to figure out. Working with an expert helped us sidestep a lot of mistakes, and the progress we’ve made in the last two years has been phenomenal.

Admittedly, Mynosys remains a very, very small company in comparison to other medical device manufacturers; we have just seven employees. But our incredibly efficient and highly experienced team has seen us do more with so much less – achieving more in just 24 months than many other projects manage with much bigger budgets, and longer time frames.

**The future**

As Zepto heads towards the market, we’ve shown the device to many surgeons who have been overwhelmingly enthusiastic, and very helpful with their feedback – Kuldev Singh even suggested the name! But the facts are that it’s inexpensive, provides what we think is a better capsulotomy than can be achieved by hand or by laser, and can do: perioperative centration on the visual axis. We don’t know for sure if or how Zepto will disrupt the femtosecond laser market, but given the proposition, you have to think that, once launched, it will make a very big impact indeed.

Figure 1: Miyake-Apple view footage shows that, compared with CCC, Zepto capulotomy results in very little zonular movement (see the video online at: top.txp.to/issues/0216/301).
Zepto: Key achievements timeline

- **2006**: Chris Keller and David Sretavan start working together on an ophthalmic medical device
- **2008**: The first Zepto-related patent is filed
- **2010**: Chris and David obtain their first grant to develop a capsulotomy device
- **2012**: A working surgical prototype of Zepto is created
- **2013**: John Hendrick and his team join the company, and the application for FDA approval begins
- **2015**: Zepto is granted a CE mark and the FDA application is submitted

**Going for Gold**

*John Hendrick, President and CEO of Mynosys Cellular Devices*

What made you want to get involved with Zepto?

I think this device is unique. After hearing about it, I commissioned some market analysis, and the data were very encouraging – I believe Zepto could become the gold standard for capsulotomy. Our competition is CCC (continuous curvilinear capsulorhexis) and femtosecond laser capsulotomy. But certain cases are problematic when using femto. Patients with small pupils, glaucoma, pseudexfoliation, for example – when you add it up, for every 100 patients a cataract surgeon sees, about 25 percent of them will have one or more of these co-morbidities.

Also, CCC and femto don’t allow intraoperative centration, which is becoming ever-more critical as the market moves increasingly towards specialty lenses – with these lenses, if you’re not centered over the visual axis, you’re going to have problems. And currently Zepto is the only device that can center on the visual axis intraoperatively. And it’s faster too – for example, it has been published that femto will add 12 to 15 minutes to the cataract procedure. Throw in the fact that Zepto costs around US$100, and I think this could become a product that every cataract surgeon will want on their shelf.

Is it time the cataract surgery had a makeover?

Yes. Capsulorhexis is an archaic part of cataract surgery. When you go to teaching hospitals, it’s the last thing they teach physicians, because it’s the most difficult. When you look at a laser capsulotomy, you realize it’s generating an enormous amount of heat – in bubbling back there! And the consequence of that is an elevation of prostaglandin levels in the eye.

Zepto is different – it doesn’t put laser energy into the tissue, and it doesn’t burn the capsule. The capsule is made up of collagen strands, and if you burn it, those strands will crystallize – and when that happens, the capsule will lose strength and elasticity. The cutting element in Zepto heats up in four milliseconds, and this causes the water molecules to expand right underneath it, cleaving the tissue. It’s a bit like the cosmetic lasers that are used on the face; they heat up the collagen and the collagen shrinks, decreasing the size of the wrinkles. In essence that’s what we’re doing, and our scanning electron microscopy work has shown that the collagen is not crystallized or burnt, it shrinks, which it what creates that small radius that we refer to as the functional edge of the capsulotomy.

What has the feedback from ophthalmologists been like?

Over the past year I’ve spoken with a lot of physicians about this device, and I’ve seen a very positive reaction; a lot of ophthalmologists are interested. It provides a fast, simple way to perform a capsulotomy, and because it doesn’t change the workflow of cataract surgery – grab this instead of your forceps and be finished with the capsulotomy in 10 seconds (although centering on the visual axis will take more time depending upon the patient) – I believe strongly that it will have great appeal.