

The MedTech STRATEGIST

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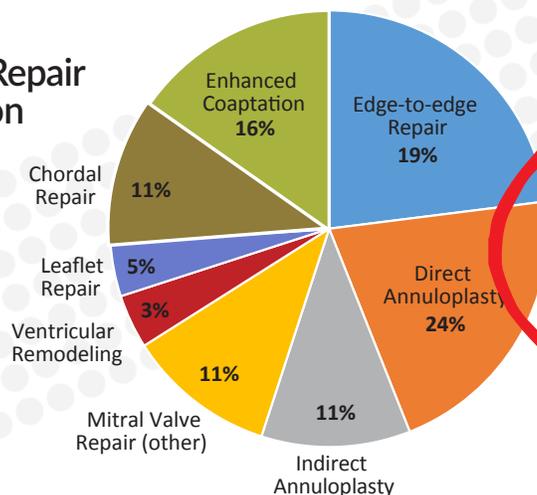
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START-UPS TO WATCH

METAVENTION:

A Device-Based Intervention
for Type 2 Diabetes
that's "One and Done"

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EDEN PRAIRIE MINNESOTA

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YEAR FOUNDED

2012

WHO'S BEHIND IT

Bobak Azamian, MD, DPhil (formerly a senior associate focused on creating the first medical device companies for Third Rock Ventures and an EIR at Versant Ventures) and Scott Vafai, MD (now at the Broad Institute, directing the development of novel therapeutics targeting the mitochondrial basis of diseases)

UNMET CLINICAL NEED

Type 2 diabetes is not adequately controlled in 50% of non-insulin using patients, despite the availability of many types of oral antidiabetic agents

SOLUTION

An interventional cath-lab procedure that achieves neuromodulation by metabolic denervation

FUNDING

\$20 million to date (Series A and B rounds) from Versant Ventures and an unidentified strategic investor

ADVISORS

Alan Cherrington, PhD (Vanderbilt University); Robert Smith, MD (Brown University); David Cummings, MD (University of Washington); Robert Rizza, MD (Mayo Clinic); John Buse, MD, PhD (University of North Carolina); John Amatruda, MD (former SVP and Franchise Head for Diabetes and Obesity, Merck); Dan Pratt, MD (Massachusetts General Hospital); Marian K. Rippey, DVM, PhD (Clinical Pathologist)

METAVENTION: A DEVICE-BASED INTERVENTION FOR TYPE 2 DIABETES THAT'S "ONE AND DONE"

Nonsurgical treatment strategies for type 2 diabetes have resulted in limited success to date; 50% of patients on oral antidiabetic agents don't achieve good control of their blood glucose levels. Metavention hopes its new interventional neuromodulation procedure targeted to cardiologists will boost success rates without burdening patients.

by
MARY STUART



Start-up **Metavention Inc.** has been stealthy these past three years or so, and that has allowed it to validate—and create substantial intellectual property around—a novel, minimally invasive device intervention for treating type 2 diabetes (T2D), one of the most burdensome diseases facing patients and national healthcare budgets today. Worldwide, almost 400 million people have diabetes, and 95% of them have T2D, a chronic disease that increases the risk of heart disease, peripheral vascular disease, stroke, kidney disease, retinopathy, and neuropathy, all of which decrease life expectancy and/or quality of life.

In the US, 10 Million T2D patients on antidiabetic drugs aren't achieving good blood glucose control.

Patients with T2D are tasked with keeping their blood glucose levels under control by consistent adherence to healthy diet and lifestyle recommendations as well as one or more oral antidiabetic drugs. This challenge is all the greater because it's largely put upon older patients—the majority of T2D patients are diagnosed between the ages of 50 and 64—who often have a lifetime accumulation of unhealthy habits.

Bobak Azamian, MD, a co-founder of Metavention (along with his peer from Harvard Medical School, endocrinologist Scott Vafai, MD) was familiar with the challenges facing those diagnosed

with T2D. He says he watched his father valiantly struggle with diet and lifestyle changes, always teetering on the edge of becoming insulin-dependent. In 2011, as an entrepreneur-in-residence at Versant Ventures, he considered the state of affairs in diabetes management. "You have all these compliance issues, all these pills and side effects that limit some of the therapies." He consulted Vafai and together the two decided to come up with a device to treat T2D.

They began by looking at the pathophysiology of the disease, at the organs that were driving diabetes, to come up with a target for intervention. They recognized the growing appreciation for the role of the gut and bariatric surgery in diabetes, but instead looked at the established understanding of the pathophysiology of diabetes in order to find a novel device target. "The liver stood out as a target that had not been addressed with devices," says Azamian, and one that made intuitive sense since the most widely prescribed drug for diabetes, metformin, addresses liver dysfunction by decreasing glucose release from the liver and influencing insulin resistance. They wondered if they could find a way to "flip the switch" by way of the sympathetic nervous system. "That's when the real work began," he recalls.

Metavention was founded in 2012 with Series A funding from Versant Ventures. Some of the funds went towards supporting sponsored research in the laboratory of Alan D. Cherrington, PhD, a professor of molecular biology and biophysics and the Jacquelyn A. Turner and Dr. Dorothy Turner

Chair in Diabetes Research at the Vanderbilt University School of Medicine, with a focus on sympathetic control of the liver, one of Cherrington's areas of expertise.

With a mechanistic hypothesis in hand—modulating sympathetic tone to stop the aberrant processes of a deranged liver—the founders developed a catheter-based procedure to permanently knock out the sympathetic nerves leading to the liver and other metabolic organs. RF energy is delivered from within the common hepatic artery with the goal of achieving a circumferential ablation that results in complete denervation of the liver and a reduction in sympathetic tone. Since the sympathetic nerves that lead to the pancreas (the site of beta cell production) and the duodenum also travel alongside the hepatic artery, “By targeting that common hepatic artery, we might have the most bang for our buck in terms of a complete denervation of the liver and very substantial denervation of the pancreas and duodenum,” says Azamian.

Metavention hopes to be able to offer an irreversible procedure that's “one and done” for type 2 diabetes patients who aren't achieving good glucose control with lifestyle modifications and oral drugs, and that applies to 50% of non-insulin using T2D patients. It doesn't replace other therapeutic strategies, it's an adjunctive therapy, but it's important to boost the success rates because, as noted, uncontrolled T2D leads to cardiovascular and other complications.

Because Metavention's therapy is novel, the company took the time to complete a series of animal studies in more than 200 subjects, including rats, dogs, and pigs, demonstrating that the procedure didn't harm the liver or the

pancreas and did not impact hypoglycemia. “We have been reassured by our safety data, which has allowed us to treat patients with this irreversible procedure,” says Azamian. Groundwork laid by companies in the field of renal denervation, which has seen some 20,000 catheter ablations inside renal arteries, also suggests that such a procedure would not damage the hepatic artery, he notes.

The company is currently in the final stages of a first-in-man dose escalation trial being conducted at six centers in New Zealand. Investigators are studying 40 patients with T2D who are on oral medications (and are not on insulin) and who have not achieved good blood glucose control despite their medications, which is the company's initial target market. The study was designed to demonstrate safety, but the company has gotten signals of efficacy as well, says Azamian.

It's a substantial first market, notes Kevin Hykes, an operating partner at Versant Ventures and CEO of Metavention, who points out that 26 million people in the US have T2D. Six million of them are on insulin, and half of the remaining 20 million—the people who aren't achieving good control—represent the company's target market. Hykes points out that the proportion of insulin-dependent type 2 diabetes patients has remained stable for over 30 years, illustrating the continuing resistance in this population to adopt insulin therapy. Furthermore, the percent of non-insulin-using patients failing to achieve glucose control has not changed in 10 years despite the advent of multiple new classes of oral antidiabetic drugs, clearly highlighting the opportunity for a new device therapy.

In the universe of medical device companies targeting T2D with an

interventional procedure, Metavention is the only one not targeting the GI specialty with endoscopic devices that act in the stomach (*see Figure 1*). The new procedure is designed for interventional cardiology, and that gives the company a natural advantage, according to Hykes. “There is an overlap between diabetes and cardiovascular disease, and significant numbers of patients with type 2 diabetes are already in the care of cardiologists.” In contrast, the referral patterns between endocrinologists and GI endoscopists placing gastric sleeves is not as straightforward.

There are more than two million cardiac catheterization procedures in the US each year and 800,000 of them are done on patients with T2D, according to the company's estimates. “These patients are naturally found in the cath labs and cardiology practices because of the cardiovascular complications that are a result of their diabetes.” Azamian says that in New Zealand, some cardiologists have already referred their patients for the clinical study. He adds, “Everyone in our space is aware of how effective the interventional cardiology community has been at developing new technologies. So if you had to pick a partner to develop something this novel, they would be the right specialist.”

There are certainly echoes of renal denervation in Metavention's liver denervation therapy. In addition to the similar catheter-based strategy to strategically knock nerves out, both disease targets (uncontrolled hypertension, in the case of renal denervation) are enormous and important in terms of the negative consequences of poor control. But Metavention's founders hope that they've taken enough precautions that the comparison ends there and the “boom and bust” phenomenon that happened

in renal denervation (i.e., promising early results, 65 companies founded and funded, then a disappointing clinical trial that burst the bubble) won't happen here. "We are operating in an adjacent space, so in some respects we do suffer from some of the headwinds," concedes Hykes.

But some things will be easier for Metavention, Hykes believes. "We are clearly treating a different disease, a different target with a different mechanism, with a much more objective endpoint." Metavention will be measuring a biochemical endpoint, the HbA1C level, whereas some measures

of blood pressure are subjective, and that is a confounding factor in blood pressure trials. "We are different enough that we think we can bring a credible approach to this therapy, which is not affected by the challenges facing renal denervation," he asserts. The company is working in a different anatomy with different flow rates and different adjacent structures. "It is different enough that it requires a specialized product that we have been able to protect," says Hykes.

And, Azamian notes that the experience of those who came before in renal denervation has helped them. "We understand the importance of understanding the anatomy before designing the therapy, we've learned from that field's experience in energy delivery, the size, shape and efficacy of different types of lesions or different types of doses, and we have understood, finally, how to design, for the FDA's consumption, a trial that will credibly demonstrate that the therapy works."

Most importantly, the company believes it has protected against fast followers—those disappointed renal denervation developers who might want to repurpose their platforms. Says Hykes, "We spent three years and a significant amount of money on a very extensive IP portfolio. We believe we have a sizeable patent estate, both in the US and internationally, that covers any possible modality of treatment, any possible target, any possible clinical endpoint, end-organ target, etc." After three years, the company is finally comfortable enough to talk about its plans, "because we have protected what we have learned," says Hykes. 🟡

Figure 1

Device Interventions in Development for Type 2 Diabetes

Company	Approach/Status
Fractyl Laboratories Inc.	<i>Revita DMR</i> , a <60 minute minimally invasive procedure targeting the duodenum, uses proprietary balloon catheters to achieve circumferential mucosal lift and hydrothermal ablation to rejuvenate the surface of the duodenum and potentially alter gut signaling in patients with metabolic disease driven by insulin resistance. 50-patient, multicenter, international clinical trial is currently underway in patients with type 2 diabetes.
GI Dynamics	<i>EndoBarrier</i> is endoscopically delivered liner situated in the intestine, just below the stomach. Creates a physical barrier between receptors in the intestinal wall and any food being digested, releasing gut hormone signals affecting insulin sensitivity, glucose metabolism, satiety, and food intake. Commercially available outside the US (company halted US clinical trial, ENDO, prematurely because of safety concerns; will seek FDA approval of a new clinical study using optimized treatment algorithms).
Metamodix	<i>EndoSleeve Gastrointestinal Bypass Liner</i> is in clinical studies outside the US.
ValenTx	Endoluminal placement of a removable device, the <i>GJBS</i> (gastro-duodeno-jejunal bypass sleeve) designed to accomplish the same three changes as the gastric bypass procedure: restriction of food intake, exclusion of food from the stomach and proximal bowel, and undigested food is presented to the jejunum. These effects trigger satiety and weight loss, and metabolic effects that decrease type 2 diabetes.
Metavention	The only interventional diabetes procedure targeted to cardiologists, rather than GI specialists; the delivery of RF energy from within the common hepatic artery is designed to achieve complete denervation of the liver. In First-in-Man studies at 6 sites in New Zealand.

Source: Company Websites