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SPECIALTY PHARMACEUTICALS

Edge Therapeutics Inc.

Local drug delivery for acute brain injury

Acute brain injury is a vexing problem for physicians. Therapeutic agents are available to treat bleeding and other complications resulting from head trauma, intracerebral hemorrhage and ruptured brain aneurysms. However, the effectiveness of these systemic agents is limited because while they may indeed stop bleeding in the brain by promoting therapeutic clotting, these drugs can also cause clotting in the rest of the body, resulting in heart attack or stroke. Similarly, vasodilators given systemically to dilate brain arteries after ruptured brain aneurysms can lead to dangerously low blood pressure.

Edge Therapeutics Inc. is working to address this problem by developing novel formulations of existing drugs that allow these agents to be delivered directly to the brain. Once applied, the bioabsorbable microparticle formulations slowly degrade, releasing drugs locally and avoiding systemic side effects.

"The whole premise is that we take off-patent and already FDA-approved medicines that we know have some effect, and reformulate them to deliver a higher concentration that is sustained for the period of time in which the medicine is needed in the brain while simultaneously avoiding systemic side effects," says R. Loch Macdonald, Edge's chief scientific officer. He notes that the approach has been used in other indications, such as delivery of anti-cancer drugs to prostate tumors via injection.

"The carrier we use is made of FDA-approved materials, so we believe the regulatory pathway will be well defined, with fewer risks than many other development programs." adds Brian Leuthner, the company's president and CEO.

Edge has an exclusive worldwide licensing agreement with **SurModics Inc.**, which manufactures and licenses a variety of sustained-release biopolymers for use in drug formulations. "Because these components are known to the FDA, the clinical development path should be more streamlined. Our research focuses on showing that the new route of administration and dosing is both effective and safe," says Leuthner.

The company's lead product, *NimoGel* is aimed at a delayed effect after brain trauma or a ruptured brain aneurysm. These conditions cause subarachnoid hemorrhage (SAH), a type of bleeding into the fluid around the brain, which can lead to delayed cerebral ischemia (DCI), typically within three to 21 days after the injury. The cause of spontaneous SAH, which usually is a ruptured brain aneurysm, can be readily treated with surgery, but the delayed effect of DCI has been more difficult to control.

Annually, about 40,000 people in the US and 750,000 worldwide are at risk for ruptured brain aneurysms, striking at an average age of 50, according to the World Health Organization. "Within 30 days, more than 75% of victims will be brain damaged or dead. These are people who are healthy and all of the sudden the next day they're fighting for their lives," Leuthner adds.

But much of the damage occurs days after the initial rupture. "The aneurysm ruptures, they get it treated, and they're okay. And then days later they have another stroke. So there's this window of opportunity in which an effective therapy can make a difference," says Leuthner.

The generic calcium channel blocker nimodipine, which dilates blood vessels, is FDA approved for prevention of DCI. When given orally or intravenously, however, nimodipine causes blood pressure to go down, limiting the dose that

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Employees: 5
Financing to Date: $2 million
Investors: New Jersey Economic Development Authority; Individual investors
Board of Business Advisors: Geert Cauwenbergh, PhD (formerly Barrier Therapeutics, formerly BioNJ); Kurt Conti (The Conti Group); Eric Hatzimemos (Hatzimemos Partners); Mike Ferguson (Ferguson Strategies); Arthur Klausner; Scott Pallais (Sentinel Hydrosolutions); Joseph C. Sanginiti (Asher Investments); Jordan Warshafsky (formerly TYRX Polymer Delivery)
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can be administered. Edge's NimoGel is a combination of nimodipine and a biodegradable polymer. The biopolymer slowly degrades when placed in the head, releasing nimodipine over the course of about two weeks. Placed at the site of the injury caused by the brain trauma or ruptured aneurysm, the drug is at its highest concentration where it's needed most. "The concentration of nimodipine is highest next to the injured brain and then becomes progressively lower as distance from the brain increases, so complications in the rest of the body, such as hypotension, do not occur," says Macdonald.

In a preclinical study in dogs, NimoGel formulation prevented DCI while being associated with no systemic side effects. "That's not achievable if you give the drug orally or by injection into a person's veins," says Macdonald. The drug does not require a separate procedure to apply because it can be administered during surgery to repair the initial trauma.

Though the exact mechanism behind DCI isn't entirely understood, it appears to be a result of multiple pathways that all share a common denominator: blood vessel constriction. Nimodipine reduces constriction by blocking calcium from entering cells through calcium channels that mediate the effect.

Some existing efforts to treat DCI have been too narrowly focused, says Macdonald. "They've singled out one pathway. But if you can block multiple pathways that contribute to poor outcome, it should increase the chances for success. Several of the pathways go through vasoconstriction."

Patients with SAH due to brain trauma and ruptured aneurysms are increasingly being treated using endovascular procedures that are less invasive than open surgery. These patients have a drainage tube and Edge has developed a formulation called *NimoVent* that could be administered through that device.

The company is also developing drugs to stop spontaneous and trauma-induced brain hemorrhages. Surgeries to remove blood clots can also cause ongoing or recurrent bleeding. Systemically delivered clotting drugs can lead to clot formation elsewhere in the body that causes death or disability that counterbalance the benefits that occur in the brain. "Instead of suffering consequences from bleeding in the brain, the patient gets side effects from stopping blood flow in the body, like a heart attack or a stroke. So we're developing drugs to stop bleeding in the head using localized delivery," says Macdonald.

EG-1964 is designed to treat chronic subdural hematoma, or bleeding between the brain and the skull. Like NimoGel, it is a sustained-release formulation. It contains the FDA-approved antifibrinolytic drug epsilon aminocaproic acid that is released over 21 days to prevent resumption of bleeding.

The company's EG-1960 is designed to prevent secondary brain damage following intracerebral hemorrhage, a result of bleeding within the brain. It is made up of a hemostatic agent that is released over three to five days.

All four products have potential sales of more than $500 million annually in the US, according to the company.

NimoGel has little competition. Oral nimodipine is now generic in the US and Europe. *Eril* (fasudil hydrochloride) is a vasodilator marketed by **Eisai Co. Ltd.** and **Asahi Kasei Corp.** in certain Asian countries. EG-1964 has no competitive treatment. The only competitive treatment for EG-1960 is supportive care, and about 90% of patients die or have permanent brain damage following intracerebral hemorrhage.

To date, Edge has raised about $1 million in Series A financing and nearly $1 million in non-dilutive funding. It just opened a Series B for $2 million, which will fund scaling up of NimoGel production for clinical trials and preparation for an NDA. The company expects to conduct a safety and toxicity study, followed by a dose escalation Phase IIa study, in 2012. Edge is focusing on NimoGel and NimoVent, and will develop EG-1964 and EG-1960 when it secures additional financing.

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– Jim Kling