

## Epygenix Therapeutics

### SUMMARY

[Epygenix Therapeutics](#) is a New Jersey-based precision medicine biopharmaceutical company established by Hahn-Jun Lee, M.Sc., Ph.D. in 2016, with technology developed by UCSF Prof. Scott C. Baraban, Ph.D. Epygenix is focused on developing drugs to treat genetic epilepsies, including Dravet syndrome, a rare and catastrophic form of intractable epilepsy that begins in infancy.

Current therapeutic options for Dravet syndrome are not effective. Patients often endure hundreds of seizures in their early years, and the constant care required places a severe burden on families. Dravet syndrome, like most genetic forms of epilepsy, represents an orphan indication with an unmet medical need.

UCSF's Catalyst Program provided funding and guidance to Baraban, who had published the first high-throughput drug screening using a zebrafish model for Dravet syndrome in 2013. Baraban combined the innovative notion of using zebrafish—which reproduce rapidly and give an early indication of whether a compound holds promise as a treatment—with the concept of purchasing libraries containing large numbers of repurposed compounds. The first round screening identified an antihistamine clemizole (EPX-100) that was approved by the Food and Drug Administration in the 1950s but was no longer manufactured or clinically available. The second round screening identified two other safely used FDA-approved drugs which treat obesity (lorcaserin; EPX-200) and sleep disorder (trazodone; EPX-300).

Epygenix Therapeutics is moving rapidly. The company received Orphan Drug Designations for EPX-100, EPX-200, and EPX-300 from the FDA in 2017, and it expects to receive orphan medicinal product designations from the European Medicines Agency (EMA) in early 2018. Epygenix is preparing to take EPX-100 and EPX-300 to clinical trials in 2018 after completing the necessary preclinical toxicology, formulation, and chemistry, manufacturing, and controls (CMC) studies.

### **A Rare Disease, A Novel Approach**

Baraban began experimenting in drug discovery with zebrafish more than 10 years ago, making a break from other scientists' traditional first line of animal testing with rodents. Rodents, especially genetically modified mice, only produce a few offspring per litter, rendering them impractical for use in large-scale high-throughput experiments. Zebrafish showed more promise: Two adult zebrafish can produce several hundred larvae at a time, and zebrafish can be genetically modified to recapitulate genetic epilepsies seen in patients.

Around 2012, Baraban, the William K. Bowes Jr. Endowed Chair in Neuroscience Research and a member of the UCSF Weill Institute for Neurosciences, received a National Institutes of Health EUREKA grant (for Exceptional, Unconventional Research Enabling Knowledge Acceleration), typically awarded to researchers exploring out-of-the-box ideas.

With that, his lab started a program to screen a zebrafish model for Dravet syndrome, an extremely rare and severe genetic form of epilepsy in children. Children with this disease "have hundreds of seizures within the first year of life," Baraban said. "Available treatments are not very effective in controlling these seizures." The seizures can start as early as 6 months of age, and children suffer delayed language and motor development skills, sleep disturbances, anxiety, and severe cognitive deficits. The risk for SUDEP (sudden unexplained death with epilepsy) is estimated at 15 times greater than in other childhood epilepsies.

Dravet syndrome is typically caused by a single genetic mutation involving SCN1A, a gene encoding a brain voltage-gated sodium channel.

The SCN1A mutant zebrafish used in Baraban's model for Dravet syndrome exhibited the same symptoms as human patients. The fish had spontaneous seizures, which responded to the same cocktail of antiepileptic drugs (AED) Dravet patients use, but did not respond to all other AEDs. The zebrafish also mimic some of the sleep disturbances, anxiety-like deficit and other motor development problems seen in these children "All the features were in place" for a validated pre-clinical model, Baraban said.

With the EUREKA funds, Baraban initiated a drug-screening program. "We screened a small, mostly repurposed drug library, with the intent that if we found something, it would facilitate a repurposing translation, rather than develop a new chemical entity," he said.

He started with a library containing 320 drugs. In 2013, his lab published a paper in Nature Communications identifying its first compound, clemizole.<sup>1</sup> “It was an antihistamine from the 1950s and ‘60s, but there was no reason to believe it would be effective here,” Baraban said. “Antihistamines are not anti-epileptic, so we figured there must be some other feature of the drug.”

Before publishing, Baraban and the UCSF Office of Technology Management (OTM) filed a patent application for clemizole as an anti-epileptic drug, to protect the intellectual property. This patent was approved by the U.S. Patent and Trademark Office in December 2017.

### **Different Paths to Commercialization**

The intellectual property filing set the stage for Baraban to start exploring how he might commercialize his findings. He had some experience in this arena: About 10 years earlier, he teamed with colleagues at UCSF to start a company, Neurona Therapeutics, out of a project in which they used mice to develop a novel interneuron-based cell therapy for epilepsy. Baraban ultimately withdrew from Neurona, preferring to focus on his work at the University.

“I like being a professor,” Baraban said. “I like running my own lab. I write my own grants. I do what I am interested in. The lab has always done translational work with the goal that somebody would then help it go to the clinic, but I have no interest in being part of one of those companies full-time.”

He also didn’t have Silicon Valley startup fever. “If we make money on it, that’s great,” he said. “But I’m not looking to be a millionaire because of something we do in my lab. I am fairly compensated and do what I love. That’s why I didn’t have any driving interest in spinning out a company personally.”

Still, he recognized that often the best way to get a therapy to patients is to do so through private enterprise, rather than from an academic lab. So Baraban sought advice, including from QB3, the Institute for Quantitative Biosciences on the UCSF campus. The options before him included:

- Start a company that would develop a drug like clemizole to treat Dravet syndrome.

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<sup>1</sup> Baraban SC, Dinday MT, Hortopan GA. Drug screening in Scn1a zebrafish mutant identifies clemizole as a potential Dravet Syndrome treatment. Nature communications. 2013;4:2410. doi:10.1038/ncomms3410.

- Start a company that would operate as a Contract Research Organization, or CRO, which would use Baraban’s zebrafish platform to conduct screening for other researchers.
- License his intellectual property to a larger pharmaceutical company, several of which had approached him about the possibility.

Ultimately, Baraban connected with the Catalyst program, which at the time was part of UCSF’s Clinical and Translational Science Institute, and now is part of UCSF’s newly formed Innovation Ventures. Catalyst offers researchers fund and advice to help get their projects to patients. Baraban’s hope was that Catalyst could help him advance the project and bring clarity on his next step.

### **The Catalyst Effect: Funding and Expertise**

UCSF, known as birthplace of the biotechnology industry, launched the Catalyst program in 2010 to accelerate the translation of research into products by providing both funding and mentorship. Catalyst offers awards of up to \$100,000 to help advance promising early-stage translational research and, almost more critically, it teams UCSF’s renowned academic scientists with experts from Silicon Valley, the biopharma industry and the venture capital world in order to spur the commercialization of laboratory innovations.

Cathy Tralau-Stewart, PhD, now Catalyst’s interim director, started working with the program in 2013 as a director of its therapeutics track. Tralau-Stewart had spent 20 years with pharmaceutical giant GlaxoSmithKline, and brought a passion for developing therapies that could help patients. Tralau-Stewart also brought an understanding of how to work with academics in her last job before leaving her native England, she had run a drug discovery program at Imperial College in London.

“I’m always stunned by the science, and stunned by how much of the science is actually translatable if someone puts the time, direction and expertise into it—and, obviously, the resources,” Tralau-Stewart said.

She particularly enjoys spending time with principal investigators, or PIs. “That is the fun bit of the job,” she said. “That’s where we, with our industry background, can really dig out the golden nuggets. By spending time with them and becoming a trusted partner of their team, they understand the value of the industry advice.”

Tralau-Stewart encouraged Baraban to apply to Catalyst in fall 2013.

### **Tackling Tough Issues**

“I was breaking it down into the options, and we had some good discussions about what they were,” Tralau-Stewart said. “It soon became very clear Scott did not want to go the platform way.” He talked to some large pharmaceutical companies, but that didn’t appeal to him either.

Tralau-Stewart could see that Baraban needed someone to help figure out the right business model, and he also needed someone to help decide the most effective progression pathway.

On the business side, she paired him with Willie Quinn, the founder, CEO and president of Bullet Biotechnology. Quinn, a former venture capitalist, had also worked at Jazz Pharmaceuticals for eight years, helping transform that company from a raw startup to a public, profitable enterprise. For the science, she brought in Andrei Konradi, PhD, a medicinal chemist and an expert in small molecule drug discovery. Konradi, a longtime scientist at Elan Pharmaceuticals and other firms, has conceived compound classes that include six drug candidates that have been tested in humans and is an author on 38 publications and an inventor of 61 US patents.

On the business side, Baraban’s concept of repurposing a drug to treat Dravet syndrome—taking it from its earlier use as an antihistamine and commercializing it—faced a few hurdles. On the surface, repurposing an old drug looks like a slam-dunk. “Everyone thinks, ‘The drug is out there, all the information’s there, it’s been in patients, we should just do a clinical study,’” Tralau-Stewart said. “Yes, you can do a clinical study, but then it’ll probably stop, and doctors will just prescribe what’s already on the market for their different types of patients. There is no commercial viability here. So you have to think through how you commercialize something like that so that you can support its development, even if your aims are not for profit.”

“Repurposing is one of the most challenging things to commercialize in therapeutics,” Tralau-Stewart said. That’s because it’s hard for pharmaceutical companies to recoup the costs of bringing a drug to market if the patent on that drug has expired. Companies need to know they’ll have intellectual property protection before they’d be willing to invest.

Scientists may employ various strategies for commercializing repurposed compounds, most commonly tweaking the compound to an improved new chemical entity with strong IP, known as a “composition of matter” patent. Repurposing for an orphan disease such as Dravet’s, which has fewer than 200,000 patients in the US, can also secure seven years’ protection, guaranteeing clinical data exclusivity for that time.

Willie Quinn, the business advisor, had experience repurposing compounds, and offered advice on how Baraban might turn clemizole into a commercializable, investable project.

“What we all want, what we're all here for, is how do you get basic research into the clinic and into patients? That's number one.” Tralau-Stewart said. “But you can't do that without the money. So you have to create a scenario where you can actually make things investable. And that means you have to have the right data, and that means a level of intellectual property ownership that an investor will invest in, or a pharma company will find interest in.”

## **Chemistry Class**

The team then began considering how it could repurpose the clemizole in order to achieve some intellectual property ownership. “You look at it and you say, ‘Can I take that compound, understand its mechanism of action, and work out what a better compound would look like?’” Tralau-Stewart said. “And that was the bit that we spent most of our time on.”

That's where medicinal chemist Andrei Konradi came in. “He did something interesting, in that he studied the chemical structure of clemizole,” Tralau-Stewart said. Konradi then advised Baraban to examine the Structure-Activity Relationship (SAR), the relationship between chemical structure and pharmacological activity for a compound.

Different compounds hit different receptors in the body. Clemizole, as an antihistamine, was designed to hit H1 histamine receptors. But it likely was hitting other receptors as well, Tralau-Stewart said, because it was having an effect on epilepsy, which has no relationship with histamines.

“Scott is a great academic neuro-pharmacologist, but industry pharmacologists look at things slightly differently, and that's me,” Tralau-Stewart said. “So, we needed to find out what else this compound did.”

She recommended using Eurofin, a CRO company, that screens compounds against many drug targets. “You get one concentration of a drug and you throw it at all of these assays,” she said. “They're very efficient and they send you a report back and typically it says where the ‘dirt’ is,” meaning it reveals what other receptors the compound is hitting other than the known target of the drug. “It's a very simple way of doing things, but suddenly you start understanding the pharmacology of the compound. Very few drugs modulate a single molecular target.”

In spring of 2014, Catalyst awarded Baraban \$45,000 to support this effort. Eurofins screened roughly 200 assays to see what else clemizole binds.

Baraban said the Catalyst guidance proved tremendously helpful. “That advice led us to a binding assay that came back with serotonin receptors as one of the hits,”

Baraban said. “So then we reverse-engineered the program. We went back and we purchased libraries for all the hits from the CRO screening— G-protein coupled receptor libraries, serotonin libraries, and ion channel libraries. We screened another 200 drugs in our zebrafish model and found two more serotonin drugs that mimic clemizole (EPX-100). Both were also FDA-approved drugs lorcaserin (EPX-200) and trazodone (EPX-300).”

On the heels of that success, Kelly Knupp, M.D., a pediatric epilepsy specialist at Children’s Hospital Colorado, administered lorcaserin (EPX-200)— already approved by the FDA as a weight-loss drug for obese people—to five children with Dravet Syndrome in 2016. Knupp received a compassionate use exemption for the trial, because of the severity of the symptoms and the lack of other treatments. Each child, ranging in age from 7 to 18 years, had tried at least five other anti-epileptic drugs without success.

Aliesha Griffin, Ph.D., a postdoctoral fellow in Baraban’s lab who worked on that collaboration project, was the lead author (with Knupp, Baraban and others) of a paper in the journal *Brain*.<sup>2</sup> (Griffin also participated in the Catalyst internship program in 2016) The Griffin, *et.al.*, paper included Knupp’s astounding results: Dravet syndrome children who had been having daily seizures for years were seizure-free, some of them for weeks at a time. A 10-year-old who had had 50 seizures a day was seizure-free for three weeks; after a cluster of seizures, the child went another two weeks without any. Another child was seizure-free for two weeks; a third had only one or two days a week with seizures.

The findings drew widespread attention beyond the Dravet community, as they broke new ground by demonstrating, according to the paper, “a rapid path from preclinical discovery in zebrafish, through target identification, to potential clinical treatments for Dravet syndrome.” To many people’s surprise, no rodents were used in this process.

## **Enter Hahn-Jun Lee**

Baraban had been hearing from various companies since his first zebrafish drug discovery paper had been published in 2013, but he was very particular about how he wanted to proceed from a business standpoint. He did not want to leave his lab or UCSF, and he was wary of partnering with Big Pharma. He met with at least 10 or 12 different companies under confidential disclosure agreements, but didn’t come to terms with any of them.

When he met Hahn-Jun Lee, M.Sc., Ph.D., however, Baraban saw a different approach that he thought would work for him. Lee was a scientist with a background in molecular biology, biochemistry and neurodegenerative diseases, and had been an

assistant professor of biotechnology at Columbia University, but he had made the shift from academia to industry.

As a biotech entrepreneur, Lee said his philosophy is simple: find intellectual property in academia that has the potential for commercialization. He looks in both the U.S. and Europe, and focuses on orphan drugs and rare diseases. “We are

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<sup>2</sup> Aliesha Griffin, Kyla R. Hamling, Kelly Knupp, SoonGweon Hong, Luke P. Lee, Scott C. Baraban; Clemizole and modulators of serotonin signalling suppress seizures in Dravet syndrome, *Brain*, Volume 140, Issue 3, 1 March 2017, Pages 669–683, <https://doi.org/10.1093/brain/aww342>

focused on niche markets, not larger indications like cancer or heart disease,” Lee said. “The most important thing is that no drug is available in the market.” He is also seeking to specialize in small molecule solutions.

Baraban appreciated Lee’s expertise in clinical development, working with the FDA and other regulators, and obtaining IP. These skills are critical complements to the work of academic scientists.

In addition, Lee has his eye on repurposing drugs. “The reason we like the repurposing strategy is, many orphan disease patients have no time to wait for the new drugs to come out,” he said. “We have to bring them out as early as possible in order to provide the best therapeutic intervention to them.”

Repurposing also saves money that would have to be spent on development, Lee said, and it also offers a safer, faster route to patients, because it is already tested in human. Using science developed in academia also brings value, in that the National Institutes of Health (NIH) and other funders have already paid for most of his research and development. Baraban pointed out: “The advantage, of course, is that all the R&D is done. I’ve already spent a decade and \$5 to \$10 millions of NIH money to get to the point where this product is. They don’t have to put any additional R&D money in because it’s already been completed in my lab here at UCSF and it was paid for elsewhere. So, all they have to do is put money in to bring it forward to the clinic.”

Lee also brings to his business a tremendous respect for academic scientists. “My approach is very straightforward: We respect scientific founders,” he said. “We actually regard all the scientific founders as equal partners to us. Our success is their success. Without their effort, this kind of breakthrough never happens.”

He looks to keep that partnership strong. “Without close work with the scientific inventor, it’s very difficult to make things move forward,” Lee said. “Our business



model is to work very tightly with the scientific inventor. We give the scientist the status of co-founder.”

Lee believes in the power of teamwork. “I always tell my colleagues that this high-tech business is like American football,” he said. “Somebody should play quarterback, and somebody should play wide receiver, but we should all remember that our end goal is touchdowns.”

Lee has started several companies on the way to this mission. He established an incubator, Curyx Partners, in Paramus, N.J., to help advance the biotechnology; and another company, Focus Therapeutics, to provide a catalytic role between US and Asian Pacific biotechnology companies via transactions and partnerships. He also founded Polaryx Therapeutics to develop patient-friendly oral medications for Batten disease, a devastating neurodegenerative pediatric genetic disorder, using IP licensed from the Rush University Medical Center in Chicago.

Baraban’s project checked all Lee’s boxes: a brand-name academic institution willing to partner, a rare disease without a treatment, and an orphan drug that could be repurposed. Lee teamed with Baraban to start Epygenix Therapeutics, licensing the intellectual property from UCSF for all three drugs Baraban’s lab had identified. Epygenix named these EPX-100, EPX-200 and EPX-300. In September 2017, Epygenix received Orphan Drug Designation from the FDA for all three drugs.

Things are moving rapidly. “Think about it,” Lee said. “We actually established the company in July 2016. I signed the licensing agreement with UCSF in September 2016. We started the clinical development in December. During this short period, we have accomplished important development milestones through teamwork and vigorous communications with FDA.”

“Specifically,” Lee adds, “we were advised by the FDA that EPX-100 can be regarded as a new drug if we repeat full IND (investigational new drug) enabling studies because EPX-100 is an old drug from the 1950s with very limited information. We are following this recommendation. Even though EPX-100 was safely used to treat an allergy 50 years ago, it is now on the new drug development path.”

Because EPX-100 hasn’t been made since the 1950s, Baraban said Epygenix is basically, with a chemistry company, following the FDA’s Current Good Manufacturing Processes (CGMP) and making high-grade EPX-100. Epygenix is then putting the EPX-100 into a pediatric formulation so that the company can start clinical trials. At the same time, Epygenix is applying for FDA approval for another drug, and if all goes according to plan, it will do human proof of principle studies with EPX-100 and EPX-300 in parallel in 2018.

### **Steering Clear of Conflicts**

Baraban was careful to avoid conflicts of interest in setting up his relationship with Epygenix Therapeutics. “Officially, I am a scientific consultant only,” he said. “They have no rights to, nor do they direct, any of my current research. The lab receives no research contracts from Epygenix. We’re fully supported by NIH and private funding.”

“There’s nothing that we do currently, or will do in the future, that is directed by Epygenix,” Baraban added. “

UCSF also places strict limits on how many hours its faculty can devote to outside enterprises, and how much money they can make as consultants. If Baraban exceeds the University limits on consulting fees, he donates it all to his department. As a faculty member, Baraban is allowed under University guidelines to maintain an equity stake in the company.

In addition to avoiding conflicts, Baraban was able to set up an arrangement that worked for him, in which he was able to stay in his lab. “I had almost no interest in pitching and raising money,” Baraban said. “I don’t mind giving up some of my ownership, because Hahn-Jun goes out and raises money, and I stay at UCSF and do my research.”

Lee had backers and had no problem raising the funds to support Epygenix, Baraban said. “The fact I didn’t have to be involved in it was the biggest part,” he said. “The fact that I don’t have to be the Chief Science Officer of the company, and I don’t have to be involved other than being a consultant, was the arrangement I wanted, versus being a principal in the company.”

If Baraban had chosen to partner with a bigger company, he feared his innovations could be lost in the process. “The big companies wanted to put me into pools of other things,” he said. “They wanted to hedge their bets and buy four or five different lead compounds and throw them together. In the end, that’s why I didn’t think it would be a good partnership.”

In addition, he said, with a big company, “I might have an idea or vision of how it works, but then I’d have to convince a roundtable of 15 or so other people who work for that company that this is the direction we should take. With Hahn-Jun, I only have to convince Hahn-Jun. So that was more appealing to me to work with a very small company that respects my expertise in this field.”

Even better, Baraban said, Lee and Epygenix are following his research discoveries to directly help patients with Dravet syndrome, which is the ultimate goal.

## **Why Catalyst Worked**

Catalyst provided Baraban with help in several significant ways. Although he already had some experience in forming a company, Catalyst provided him with industrial pharmacology, medicinal chemistry and commercialization expertise.

On another level, Catalyst recognizes that no one person—even a brilliant scientist—can know everything needed to get a company off the ground, or a drug to market. Sometimes business expertise is needed; sometimes a different scientific perspective does the trick.

“Scott’s not a drug development pharmacologist, and I’m not a neuroscientist,” Tralau-Stewart said. “I think the two mix quite well. To me it’s a great example of academic experience and knowledge working with industry to find a way forward. The collaboration with Hahn-Jun Lee further illustrates the power these academic-industry collaborations”.

Catalyst provided money for Baraban to conduct his screens, but that wasn’t the program’s chief benefit. Simply suggesting to Baraban that he hire a contract research organization to run those screens was the real value.

“The money itself, in my case, was incidental, because the laboratory is relatively well-funded,” Baraban said. “Even if they came to me and said, ‘Spend your own money on the Eurofins screen,’ I would have spent the money. It’s just good advice.”

The advisors taught Baraban that it wouldn’t even make sense for him to run safety trials in his lab, because the FDA will want to see them run by an independent CRO anyway. Advice like that saved him time and money.

That advice came from Konradi, the medicinal chemist, and led directly to some of Baraban’s greatest successes. Quinn’s business-oriented advice was also helpful, Baraban said, even though Baraban didn’t follow his suggestions to start a company. “It was also good to hear his opinion on what was the positive or negative of starting a company,” Baraban said.

Having already gone through one startup, Neurona Therapeutics, without the benefit of Catalyst advice, Baraban grew wistful thinking of what might have been.

“I would have loved to meet all of them when we started Neurona, to be honest, and learn about it from the beginning,” he said. “All of us would have benefited from that.”

Catalyst also runs “report out” events in which other scientists present their work. Baraban appreciated learning about other cutting-edge science going on at UCSF that he might not otherwise have known about. And each one talked about how they

are trying to get out of the lab and into a patient-facing therapy, so he learned different translational strategies.

In addition to his initial grant, Baraban returned to the Catalyst Plus program in the fall of 2017 and was awarded another \$100,000 to support his latest grand research ambition to generate mutant zebrafish lines for all known human epilepsy genes for the development of new precision medicine based therapies.

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