A FAMILY RACES THE CLOCK

Lucy Landman has a disease so rare it affects only a few dozen children worldwide. Can a biotech entrepreneur's radical approach engineer a treatment in time?

BY RON LEUTY
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Little Lucy Landman was a laughing, playful child just slightly off the development milestones for a 5-month-old when her parents set up a visit with her pediatrician last fall. ¶ It was the start of a process that led to a startling diagnosis of an extremely unusual condition, one that has put Lucy and her family into an ongoing race against a progressively debilitating disease that afflicts just a handful of children globally. Along the way, their path intersected with Bay Area biotech entrepreneur Ethan Perlstein, who has made it his mission to repurpose drugs from thousands already approved and use them to treat some of the rarest of rare diseases.

Perlstein's approach is unique. He works with families of children with genetic diseases to self-fund drug discovery and, ultimately, drug development. Not even Bay Area rare disease drug pioneers such as BioMarin Pharmaceutical Inc. and Ultragenyx Pharmaceutical Inc. target such tiny populations. For the tens or hundreds of millions of dollars companies put into developing a new drug, there's little chance of getting a return on investment with such a minute number of patients.

Yet Perlstein and his public benefit company, Perlara, continue to pursue repurposed drug projects for families willing to put up hundreds of thousands of dollars to secure a measure of hope.

In at least one case, the approach is showing a result. Late last year, a joint venture between Perlara and a nonprofit started by the parents of an 8-year-old Michigan girl with a rare disease scored regulatory approval to start a late-stage clinical trial. Through its drug-screening platform, Perlara identified an oral compound initially designed 30 years ago in Japan for common diabetic nerve damage.

That venture, called Maggie's Pearl LLC, is the only spinout company to date under Perlstein's model, but Perlara is working with 30 families or foundations in all.

"I suspect there will be more than a handful of potential Maggie's Pearls emerging, but more like next year," Perlstein said.

Enter Lucy, who was diagnosed in April with a genetic condition that causes her body not to produce enough of a protein that is key to developing skills such as speech and sitting upright. By the age of 4, she could develop intractable seizures.

Lucy's parents, Geri and Zach Landman of Danville, have raised more than a quarter-million dollars from friends, family and well-wishers to support the efforts of Perlara's network of moonlighting scientists to build a yeast model of Lucy's condition. Then Perlara tries to match the disease to one of thousands of already-approved drugs.

It's not a simple – or cheap – process.

The Landmans, however, are committed to finding a treatment for their now-14-month-old daughter before it's too late.

If Perlara can link the disease to an existing drug that could be relatively quickly repurposed for Lucy, they hope she can recover some of the skills she's already lost.

Zach and Geri Landman with Lucy, now 14 months, who was diagnosed in April with a rare genetic condition

"It's truly a logistics problem," Zach Landman said. "When your child is metaphorically dying – their brain is dying in front of you – you don't let logistics stay in the way."

A rare diagnosis

Save for an excessively sleepy first two weeks after she was born in late May 2021, Lucy seemed like most other infants. She batted at toys and appeared otherwise physically and cognitively in line with

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the milestones that many parents of infants religiously track.

But at four months, Geri Landman said, Lucy seemed "floppier" than the Landmans' older daughters were at that age.

Lucy's parents have a heightened sensitivity to blips on a medical chart: Geri is a pediatrician; Zach is a pain medicine specialist. So instead of waiting for a six-month checkup with Lucy's pediatrician, they scheduled it at five months.

They were referred to a neurologist, who said Lucy was slightly hypotonic – a state of abnormal muscle tone – but believed that with physical therapy she would largely catch up to her peers by the time she turned 1.

But toward the end of a family vacation not quite four months later – earlier this year – Lucy's condition started to deteriorate. She couldn't hold herself in a sitting position, her trunk bent forward or to the side.

What's more, her babbling baby sounds had subsided, she wasn't making eye contact and she stopped eating.

The Landmans wound up March 7 in a hospital emergency room. Within eight hours, Lucy was discharged with no new insights. But the Landmans on March 21 sent videos of Lucy to her neurologist, who then had her admitted that night for an expedited workup at Stanford's Lucile Packard Children's Hospital.

Lucy had her brain scanned with magnetic resonance imaging. Her spine was tapped to extract cerebrospinal fluid to look for telltale signs of infection or indications her neurotransmitters – the chemicals that deliver messages between neurons – weren't firing like they should. She received an electromyography, or EMG, to assess her muscles and the motor neurons that control them. Her brain waves were tested with an electroencephalogram, or EEG, to try to detect any seizures.

All were normal. After three days, Lucy inexplicably returned nearly to her baselines in strength, eye contact and smiling and was set to be discharged.

But Dr. Maura Ruzhnikov – a pediatric neurologist and geneticist with Stanford Children's Health who by chance was doing patient neurology consultations at the hospital that week – wanted to learn more. She ordered a set of genetic tests for Lucy who was by then back to eating solid foods and sitting up.

On April 18, Ruzhnikov texted the Landmans: "Lucy's genetic tests are back and I'm concerned," she wrote. "Let's meet in an hour."

The tests showed that Lucy has two bad copies of a gene called PGAP3, a combination found in only 35 to 50 kids globally. Each parent gives one bad copy and one normal copy of the gene, but in PGAP3 disease, the two bad copies come together in an ill-fated roll of the genetic dice known as autosomal recessive inheritance.

PGAP3 disease typically isn't fatal, except in the most-severe cases, but it can be life-defining: In addition to low muscle tone, it causes moderate to severe intellectual disability and developmental issues similar to autism. Patients never develop expressive speech and by 4 years old may have tough-to-control seizures.

Most children with PGAP3 disease are diagnosed when they are 4 or 5 years old, after seizures start and doctors look for genetic causes.

Lucy's early diagnosis provides an opportunity to find a drug that could make a difference for her.

If a treatment is found, the thinking is, an infusion once a day, week or month might boost Lucy's protein levels to help her gain skills – maybe even regain skills – and live a normal life.

But every day without a treatment could lock in the disease's effects permanently.

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'Time is brain'

With some of the cash the Landmans have raised, Perlstein's network of researchers are trying to match Lucy's genomic data to a drug, one of the 5,000 to 6,000 approved over the last 100 years for a vast range of diseases or conditions.

Repurposing could shave years off a new-drug discovery and development process that often takes upward of 10 years and carries a price tag of $1 billion or more.

"Earlier is better – or, as we often say, 'Time is brain,'" Zach Landman said. "If we correct it at 1 or 2, do you prevent autism features from developing?"

Soon after Lucy's diagnosis in April, Ruzhnikov alerted the Landmans to families of other children with diseases similar to Lucy's who had tapped Perlara's model to find drugs. One of those was the family of Maggie Carmichael, the Michigan girl whose parents employed Perlara to match her condition to a drug.

When Perlara finds a hit, Perlstein moves from drug-discovery mode to drug development. In the case of Maggie, that led to Maggie's Pearl, a joint venture between Perlara and a nonprofit started by her parents. The idea is to find a drug, lock in intellectual property rights for the specific disease and secure a priority review voucher from the Food and Drug Administration. Such a voucher could be sold to another drug company for millions of dollars, allowing the buyer to expedite FDA review of another drug for which it is seeking agency approval.

But first, Maggie's Pearl must show that the drug works. It got the green light from the FDA in December for a clinical trial of a drug, called epalrestat, developed 30 years ago in Japan for diabetic nerve damage. The Mayo Clinic in Minnesota will oversee the late-stage, placebo-controlled study in 40 patients that could begin next month.

"Our goal is to do that with Lucy," Zach Landman said.

This is how it works: Using a report from the sequencing of Lucy's exome (the pieces of DNA that contain the instructions for making proteins), Perlara's team is using off-the-shelf yeast to create an avatar of her dysfunctional gene. From there, Perlara hopes to undertake an initial screen of drugs, then use more-directed yeast or more-complex organisms, like worms and flies, to further narrow the list of drugs that could work.

Perlstein, a 42-year-old, Harvard-trained Ph.D., said he's careful not to overpromise what Perlara can deliver. But he hopes to launch five yeast programs over the next five months to generate proof-of-concept data.

"We're trying to see if the playbook is reproducible" from person-to-person and disease-to-disease, Perlstein said. "I hope we do this enough times that [researchers] will trust the yeast."

It's gumshoe medicine, Perlstein said, that could expose single-use drugs to many potential uses.

Ethan Perlstein, Perlara: "Repurposing is the most wonderful thing we have in medicine."

"Repurposing is the most wonderful thing we have in medicine. The first purpose may not be the best purpose," he said. "There could be more hits."

Indeed, said rare disease specialist and Ultragenyx Pharmaceutical CEO Emil Kakkis, repurposing existing drugs can be useful, especially for diseases with a common pathway.

Although he said he didn't know much about Perlara's model, Kakkis pointed to the case of Dr. David Fajgenbaum, a University of Pennsylvania assistant professor in translational medicine and genetics who had a rare and often fatal lymph node condition called Castleman Disease; Fajgenbaum in 2014 started testing an already-approved drug for kidney transplant patients on himself to counteract an overactive immune system caused by the disease.

"For some enzyme deficiency disorders, it is much [more difficult] to get good effects from repurposed drugs but not impossible," Kakkis said. "So the model can work."

Perlstein relies on a crew of

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THE SCIENCE OF PGAP3

The post-GPI attachment to proteins phospholipase 3 gene — the full name for PGAP3 — normally encodes an enzyme, a type of protein that is essential for many functions in the body.

When the gene expresses the protein correctly, the enzyme modifies fatty acids — lipids called glycosylphosphatidylinositols, or GPIs — that anchor molecules to cells and allow cells to communicate with each other. But in the case of the PGAP3 condition, mutations to both the mother's and father's copies of the gene are combined and the protein isn't produced or is produced at insufficient levels. The signaling molecules don't settle onto cells and messages between cells get garbled.

The disease is, as Geri Landman described it, the difference of a single amino acid — the molecules that combine to form proteins — in a single protein.

With Lucy Landman, enough protein had been produced in her first few months to interact with her family, sit up and play with toys. But those levels are unsustainable, so her skills can decline. Her body may never produce enough of the protein.

That is, unless a drug can be found to boost the protein to a sufficient level for her to learn new skills and, perhaps, regain skills.

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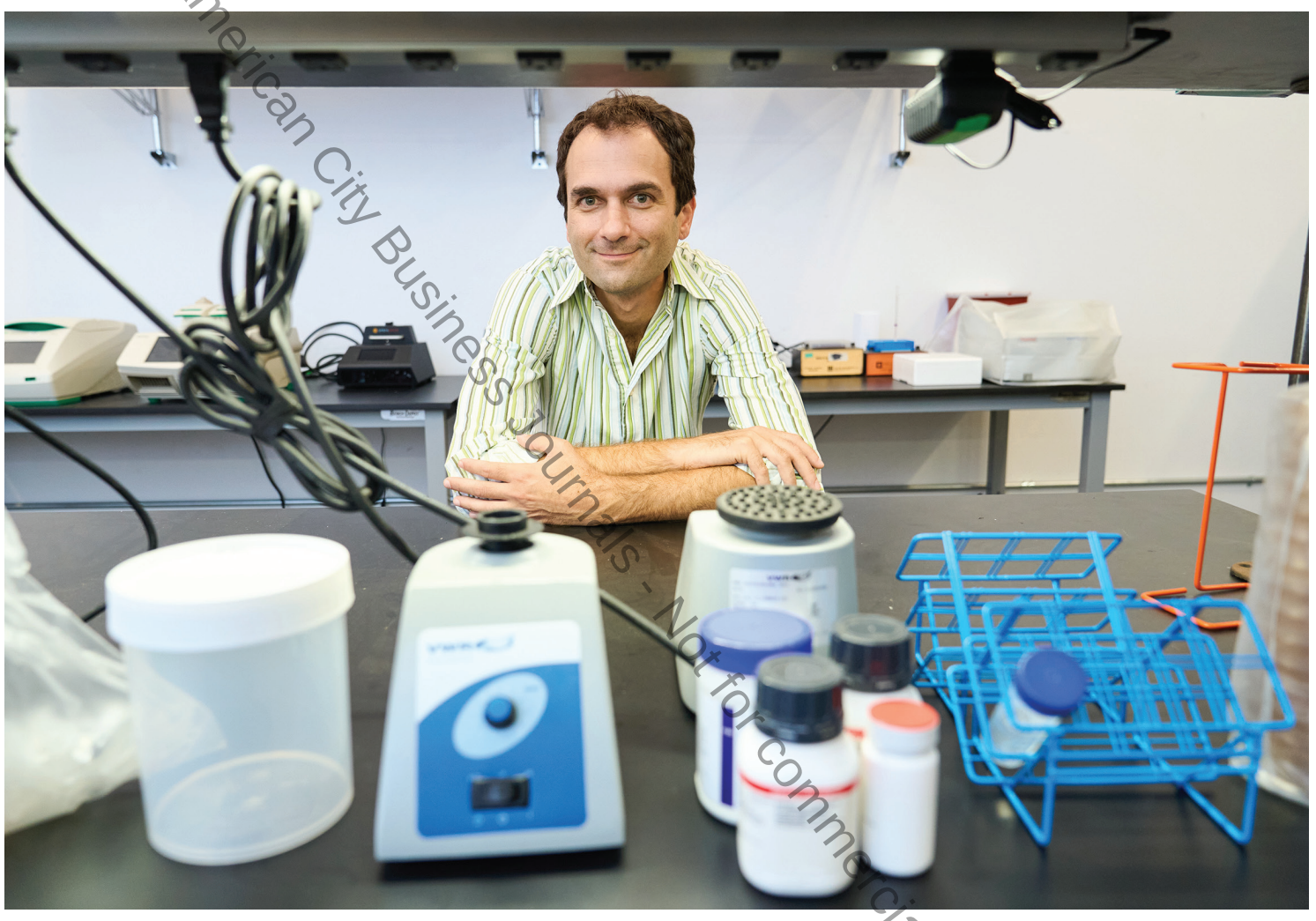

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"cure guides" that may put in a couple hours every couple of days to grow yeast, for example. It's like a WeWork for cures, Perlstein said, with the guides coming from day jobs in labs at Stanford and the University of California, San Francisco.

Those guides use a lab bench and shared equipment in incubator space rented by Perlara since May near Zuckerberg San Francisco General Hospital. They're cooking up yeast for Lucy's disease or creating fibroblasts, a protein-secreting fibrous cellular material, for a Mexico City family with a connective tissue disorder, updating the team via the Slack messaging app.

The money raised by families pays for the cure guides Perlstein manages, the lab space and buying yeast and other materials.

"A VC doesn't want to fund a low-profit drug company for maybe dozens of ultra-rare disease patients," Perlara said. "It's not a market failure, but it's a failure of other parts of the market not realizing the model is there."

The model is in progress. Perlstein has continued to tweak it since creating the original Perlara eight years ago, staking the company with $2 million from angel investors, a San Francisco family with a daughter with a rare disease and a cold call by Perlstein via Twitter to hedge fund manager Martin Shkreli.

The initial Perlara was shut down after Perlstein became chief scientific officer at the Christopher & Dana Reeve Foundation, but that lasted only eight months until spring 2020.

Shkreli, who would be convicted of unrelated securities fraud in 2017, was later bought out of Perlstein's venture. Swiss drug giant Novartis AG and billionaire entrepreneur Mark Cuban would later invest, though Cuban said in an email that he hasn't been involved with Perlara "for a while."

Perlstein doesn't plan on taking on new outside investors, he said, adding that Perlara is operating sustainably on money from families or their nonprofits.

Raising the cash

The Landmans, also parents to 8-year-old Audrey and 5-year-old Edna, started a GoFundMe page aimed at raising about $100,000 to back Perlara's efforts on behalf of Lucy.

To date, 461 donors have contributed $78,185.

Meanwhile, the family also is working with researchers at Nationwide Children's Hospital in Columbus, Ohio, pursuing one-shot-and-done gene therapy, where a correct copy of the PGAP3 gene could be injected into Lucy.

Development of a gene therapy takes more time and more cash – closer to $3 million, the Landmans estimate – just to get to the point of an early-stage clinical trial with four children. For that effort, the Landmans started a nonprofit, called Moonshots for Unicorns, that has raised about $165,000 with commitments to date that would push it over $200,000.

"Lucy is our unicorn baby," Zach said.

Yet if Perlara finds an existing drug that could be taken daily, weekly or monthly to boost the protein expressed by the PGAP3 gene, that route likely would offer a quicker, cheaper and meaningful fix for Lucy's condition before it worsens.

"We need to get the protein boosted in Lucy's cells like yesterday," Zach said. "We don't need discoveries in academia in five to 10 years. We have months."

RARE AND ULTRA-RARE DISEASES

- *Seven thousand rare diseases have been identified*
- *The Orphan Drug Act defines rare disease as affecting fewer than 200,000 parents in U.S. Europe uses a similar standard of about one patient per 1,500 people. While there is no official statistical definition for ultra-rare diseases, some researchers define it as a condition affecting fewer than one per 50,000 population.*
- *Together rare diseases affect an estimated 25-30 million Americans*
- *95% lack an approved FDA therapy*
- *UCSF and Benioff Children's Hospitals are among 31 designated Rare Disease Centers of Excellence in the U.S.*
- *Rare disease resources: The Genetic and Rare Diseases Information Center (GARD); National Organization for Rare Disorders (NORD); Rare Diseases Clinical Research Network.*

SOURCE:National Institutes of Health, GARD, NORD

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Geri and Zach Landman, both in the medical field, launched a GoFundMe to raise money to pay for Perlara's efforts to find a drug for Lucy. They also started a nonprofit to raise funds to develop a gene therapy.