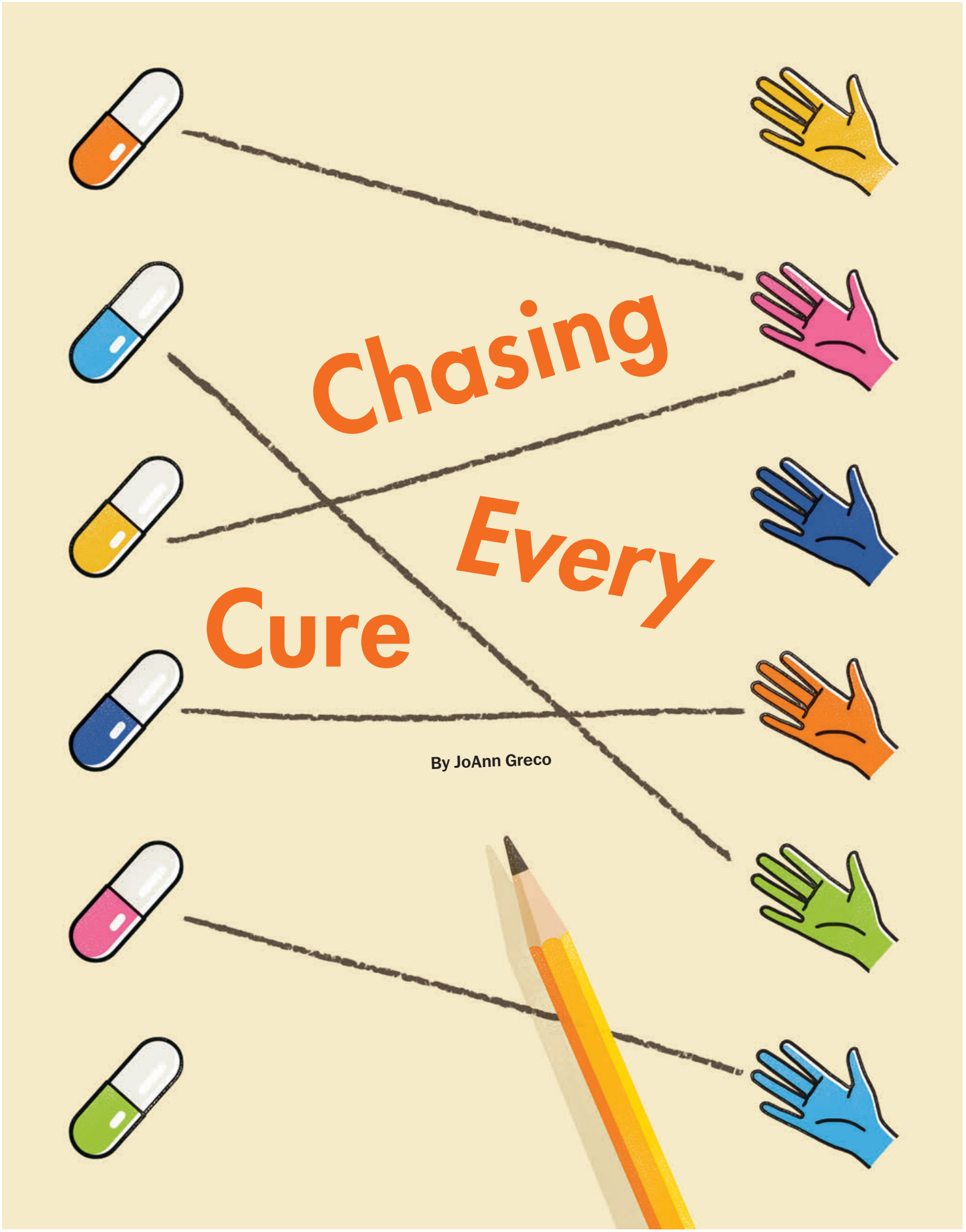

Chasing Every Cure

By JoAnn Greco

His patient wasn't doing well, and Luke Chen was out of ideas. "We had tried every medication under the sun known to work with his disease," recalls Chen, a clinical hematologist at the University of British Columbia at the time. "The treatments would work for a few months, then things would devolve again. It got to the point where we were at the end of the line."

It had all started two years before, when Chen's patient, a busy Canadian surgeon, suddenly developed severe abdominal pain and fever. After three days of extreme pain, and with no sign that his symptoms were alleviating, the 47-year-old made his way to the emergency room and was admitted to the hospital. Tests revealed that his blood work was abnormal; a series of scans eventually revealed diverse enlarged lymph nodes.

After a biopsy, the patient at last received a diagnosis of idiopathic multicentric Castleman disease (iMCD). Diagnosed in fewer than 5,000 Americans a year, Castleman is characterized by enlarged lymph nodes in multiple regions of the body along with flu-like symptoms. In some cases, the disease can result in organ failure due to an excess of inflammatory proteins known as cytokines.

From onset to diagnosis took about four weeks. What followed was a years-long ordeal for the patient. Finally, with talk of palliative care hanging in the air, Chen placed a desperate, last-ditch call to Penn's David Fajgenbaum M'13 WG'15, a medical colleague whose successful quest to cure his own case of Castleman Disease was recounted in his dramatic 2019 memoir *Chasing My Cure* ["Views," May|Jun 2020]. It would prove a most surprising chat, and one that offered a ray of hope for his patient.

Fajgenbaum told Chen that his team at Penn's Cytokine Storm Treatment & Laboratory (CSTL) had recently found that some iMCD patients exhibited elevated levels of a protein called tumor necrosis factor (TNF). Further, by using machine learning they had identified a drug that might work for these patients. The drug, called adalimumab (commonly known as Humira), was a protein-inhibitor that was already FDA-approved to treat inflammatory conditions like rheumatoid arthritis, Crohn's disease, and psoriasis.

The news was an eye-opener for Chen—and a bit of a head-scratcher. "Not only was TNF not previously thought to play a significant role in Castleman," he says, "but it had never crossed my mind to use a TNF-inhibitor—because they're not that strong and I had used much more potent drugs that hadn't worked." Chen agreed it was worth a shot, though he wasn't expecting much of an effect. But within a few weeks of taking the drug, his patient was in remission. That was two years ago, and he continues to do well, taking adalimumab once a week, via subcutaneous injection.

When David Fajgenbaum unlocked his own treatment after being diagnosed with a rare disease, he saved his life. Now he has his sights on a higher purpose that's bringing hope to millions.

"In theory, it would be great to try and get adalimumab approved" for use as a treatment for Castleman, says Chen, who is now a professor of medicine at Dalhousie University in Halifax. "But this would require a prospective clinical trial that costs tens of millions of dollars to run. And we would probably only use it for less than 100 patients a year in North America, whereas there are many thousands of patients on the drug for its currently approved indications. So the economic numbers don't add up."

Even if the trial was done, he adds, "the drug company would then have to bring that new indication to the FDA—or Health Canada in our case—for an approval, which is another step that takes months to a year and costs many millions." Given these hurdles, "you can see why it's very hard and uncommon to get drugs approved specifically for rare diseases like Castleman," he says.

Soon after this encounter, Fajgenbaum invited Chen to serve as an advisor for Every Cure, a nonprofit he has launched devoted to using artificial intelligence (AI) to help identify existing drugs that can be used beyond their original intent to help patients with rare diseases that for the most part currently have *no* FDA-approved treatments. The story of Chen and his patient was recently published in *The New England Journal of Medicine*. But more than a case study, it offers "proof of the power of combining lab research with AI-driven insights to uncover hidden cures to save lives," Fajgenbaum says. "The potential of repurposing existing drugs is enormous, and we're just getting started."

Repurposing isn't a new idea. Sildenafil, the active ingredient in Viagra, was originally developed in the 1980s to lower blood pressure but quickly morphed into a treatment for erectile disfunction, receiving FDA approval for that use in 1998. And just two years ago, the FDA approved the same molecule (under the brand name Revatio) as a treatment for a rare pediatric lung disease. Another prominent example of repurposing—as anyone watching television knows—are the several drugs originally used to control diabetes that have received approval as weight loss aids. Ozempic, while perhaps the most well known of this class (semaglutide), has not

ILLUSTRATION BY CHRIS GASH

yet been approved for the new use (and thus cannot be explicitly marketed for it). Since it has been approved by the FDA for *something* (as a diabetes treatment), however, doctors are legally allowed to write a prescription for it. This practice is known as "off-label" use.

Over the last decade, Fajgenbaum, who is also an associate professor of translational medicine and human genetics at the Perelman School of Medicine, and Grant Mitchell M'14 W'14 have watched these developments with interest. "We began asking, 'Why isn't this happening regularly and automatically?'" Fajgenbaum says. "And we learned a few things. One is that there are very limited incentives. First, of course, is that the market for any rare disease is by definition so small that the profit motive isn't there. Also, since more than 80 percent of drugs are generic, even if sales were to skyrocket, there are so many players that profits would be split and split again. That was a heartbreaking realization. Another thing is, there has never been an easy way to quantify and assess all of the approved drugs out there—the tools and technology didn't exist until AI came on the scene. Lastly, no one central organization is responsible for making sure that these drugs are being used in as many ways as possible."

To provide solutions, the two cofounded Every Cure in 2022 along with Tracey Sikora (who in October became vice president of research and clinical programs at the National Organization for Rare Disorders). Incorporating as a nonprofit, they planned to use new AI tools to identify possible matches between the world's 18,500 or so recognized diseases (less than a quarter of which have FDA-approved treatments) and some 4,000 drugs. By partnering with academic groups and other nonprofit organizations, Every Cure aims to serve as a central clearinghouse to share the information it gathers.

"What Every Cure does is make a big tent for the thousands of rare diseases out there," Chen says. "Clinicians like me who see lots of patients with variations of these diseases are part of that. We're not looking for one treatment, we're looking for everything that may be used. If it's another weapon in the arsenal, it's a win. With a repurposed drug, toxicity and risks are already well known. Repurposing is an understanding that viewing a drug as good only for gastroenterology, say, or rheumatology, is creating a totally false boundary."

The big question is "whether insurance companies will cover the new use" once the disease-drug matchup is identified, Fajgenbaum says. "So we need evidence. For us, it's all about generating that evidence."

Exhibit A for the potential behind Every Cure's ambitious goal has always been Fajgenbaum's own terrifying and riveting story. Diagnosed with iMCD while still in medical school, he came very close to dying five times in three and a half years, before deciding that it would be up to him to ensure that there wouldn't be a sixth time—a process he describes in *Chasing My Cure*. Plans are under way for a film version of the memoir, according to recent announcements.

Mitchell, who met Fajgenbaum on their very first day of medical school, has the real-life scenes from his friend's harrowing experience embedded in his mind. He still sounds astonished by the rapidity of what unfolded one summer day in 2010, in the third year of their medical training. "David went from being an unbelievably fit person, in peak form and vitality, bench pressing 300 pounds, to walking into our apartment and saying, *Man something is wrong, I just feel like I'm going to die,"* he recalls. "Medical students are notoriously hypochondriac—we're always diagnosing each other—so I was, like, *Calm down*. Boy, was I wrong. He was in a coma fighting for his life in a matter of weeks. The good news is he survived. The bad news was that there was very little information on this disease."

But Fajgenbaum was well equipped to surmount that difficulty. Before starting medical school, he had earned a master of science degree in public health at Oxford University. His dissertation, researched with a prescience that would come in handy later, concerned the lack of coordination and cooperation among researchers. "The biggest takeaway from that time was to not think about healthcare only on a doctor/patient level, but also on a systems level," Fajgenbaum says. "That can mean the environmental factors that come into play in the development of an illness, for instance. It's about considering the problem and seeing all the variables." The effort to think systematically to solve big problems has guided him throughout his career thus far, as he has worked toward breaking down the frustrating barriers between specialties, drugs, and diseases.

Mitchell, with his own training at the Perelman School and Wharton, was also intrigued by the idea of combining insights and approaches from medicine and business. Fajgenbaum's illness presented an opportunity to put their shared interest to work. "We had the advantage of being young and naive and thinking we could do something about getting to the crux of Castleman," Mitchell says. "We were trying to figure out what research was available, and we kept using this term *they*. What did *they* know? How could we reach *them?* But as we got deeper in trying to wrestle with the problem, we started to realize that *they* weren't really out there. It was a very imperfect network of half solutions and partial collaborations, and we looked at each other and said, 'Could we be *they*?' And that was what ignited him on this warpath."

That path would impel Fajgenbaum not only to read everything on Castleman that he could get his hands on, but to conduct experiments on himself—which, as he notes in his book, scientists have done for ages (including 12 Nobel Prize winners). In 2011, while

Perfect match: Fajgenbaum (right) and Every Cure cofounder Grant Mitchell, a close friend and experienced entrepreneur in the health field.

working as a staff member of the newly formed Penn Center for Orphan Disease Research & Therapy (now Orphan Disease Center) ["Gazetteer," May|Jun 2021], Fajgenbaum learned that "although each particular disease might be rare, the collective numbers are astounding."

More than 300 million people around the world are afflicted by one of more than 10,000 diseases that are characterized as rare, only a handful of which, like cystic fibrosis and amyotrophic lateral sclerosis (ALS), aka Lou Gehrig's disease, are familiar to most people. According to Every Cure, 95 percent of these diseases have no recognized treatment, and they receive but a fraction of research and development dollars. In 2023, for example, just 14 percent of rare diseases attracted National Institutes of Health funding.

During his quest to learn everything about Castleman, what Fajgenbaum mostly discovered was how little there was to know. "Five and a half decades had passed since Dr. [Benjamin] Castleman reported the first cases [in 1954]," he wrote in *Chasing My Cure*, "but the cause, key cell types, and key cellular communication lines were all unknown; the only breakthrough was the finding that IL-6 [a cytokine] production is in overdrive, which came from a few studies of a few iMCD patients."

During his quest to learn everything about Castleman, what Fajgenbaum mostly discovered was how little there was to know.

The young medical student ultimately found his way to the only lab in America dedicated to studying Castleman, run by Frits van Rhee at the University of Arkansas. Dr. van Rhee helped get Fajgenbaum an experimental dose of siltuximab, a new drug then still in Phase II of a randomized controlled study—the first such clinical trial for iMCD ever. Siltuximab ultimately received FDA approval to treat iMCD in 2014 and it remains the only official treatment. But as was the case with Fajgenbaum, many Castleman patients do not respond to it as a first-line treatment.

Soon enough, he was sicker than ever, more terrified than ever, more frustrated than ever. Facing Round Four of his fight with Castleman, Fajgenbaum wrote, "the only thing the medical community 'knew' about iMCD was not correct for me." He made a vow. "If I survive this, I'm going to dedicate the rest of my life—however long that may be—to answering these unknowns and curing this disease."

During his illness, Fajgenbaum had become aware of two foundations that provided referrals to a small group of doctors and generated awareness and some research funding—neither of which,

Photo by Michael Branscom

however, was working to bring together the research community in any substantial way. "This effort to cure Castleman disease would be a challenge for a leader as much as for a researcher," Fajgenbaum wrote. "I set out to become both. I wasn't going to reform any existing structures. I was going to build something new."

For support and guidance, he enlisted van Rhee as cofounder of what became the Castleman Disease Collaborative Network. Within a few years, CDCN had "developed diagnostic criteria, developed a very large network of scientists around the globe who hadn't been working together, developed treatment guidelines, and developed a research agenda," van Rhee observes. "And, all the while, of course, we served as a way to bring together patients."

In late 2016, after years of applications and advocacy, Castleman finally received its own unique medical billing diagnostic code, enabling experts to better analyze trends and to collect more accurate data. Meanwhile, on the way to understanding Castleman, the network's research has also been instrumental in further unlocking the mysteries of the immune system and autoimmune diseases. "David is a very outstanding individual, and he's accomplished a lot in a relatively short career," van Rhee says. "For him, the sky is always the limit."

As he vowed, Fajgenbaum succeeded in finding his own treatment. He did so by addressing what he believes is a core problem plaguing medicine: you can see only what you look for. He reexamined his bloodwork and medical records multiple times, keeping an eye out for missed signals and overlooked clues. Crucially, he flipped his approach to understanding just what exactly was happening to him during his life-threatening bouts with iMCD. It all came together when he realized that, rather than a disease of the lymph node, his might be an immunity disorder—and, if so, an immunosuppressant created for another set of patients might help.

In February 2014, Fajgenbaum began taking sirolimus—a drug that had been used for 25 years to prevent organ rejection after kidney transplants—and he hasn't had a relapse since. With a new reason to look forward, he and his longtime love Caitlin Prazenica married later that year, and they are now the parents of a three-year-old and a six-year-old.

"I just feel so grateful and very optimistic," Fajgenbaum says. "My experience no longer creates anxiety. Over time, that anxiety has transitioned to urgency—urgency for solutions that can help thousands. I'm focused on the end goal of identifying new treatments." How many FDA-approved drugs are out there, ready to be used for treating many more diseases than they already were? Fajgenbaum has wondered this ever since he first entertained the idea of the CDCN. It's a "line of questioning that I would never again put down," he wrote in *Chasing My Cure*. "I became consumed with the idea."

In forming Every Cure with Mitchell, one of his best friends, the researcher has found his perfect match. A serial entrepreneur, Mitchell launched two start-ups while still a student at Penn. The first was a patented technology now marketed as Adhere Tech, which tracks dosages, reminds patients to take their meds, and intervenes if they miss a pill. The second, the app Curbside Care, was an early attempt at "Uberizing" medicine by tapping into the regional network of hospital shift workers who might be interested in making themselves available for house calls during off-duty hours. That one didn't do as well, "probably because it was a little ahead of its time, in light of what happened with telemedicine," Mitchell says. After graduation, Mitchell joined the international consulting firm McKinsey & Company, delving further into how data could be used to improve patient outcomes.

Every Cure's approach hinges on large language models (LLMs) that pull information on biomedical concepts—a drug, a disease, a gene, a tissue, a protein—from semantic sources like medical journals and databases and compilations. It then constructs a 'knowledge graph' that attempts to capture all of that information and examines it to find plausible new connections between existing drugs and diseases with unmet needs. In doing so, the organization is pioneering a new field of research called computational pharmacophenomics, visualized by the knowledge graphs that show lines connecting millions of nodes to each other, where every node is a biomedical concept and every line is a relationship between nodes. So, you might see one line between a drug and a disease, another one connecting that drug with reducing elevated protein levels, and another linking the same protein expression to another disease. The intersections can unlock pathways toward treating a rare disease with no known treatment.

"The beauty of this approach is that you can integrate knowledge from multiple modalities," says Mitchell. "The graph itself isn't raw data; it's the abstraction of knowledge and relationships found in raw data then representing the entirety of that knowledge in one place."

Every Cure started with preexisting knowledge graphs that were funded by the National Center for Advancing Translational Sciences (NCATS) and has enhanced them so they can be combined and layered. In addition the graphs have been enhanced with embeddings that use generative AI to incorporate more nuanced information about each node and edge. Now, instead of a single node being just "aspirin," for example, information on its molecular structure can also be included, widening the field for the machine learning algorithms to make new associations.

"Our technical and IP strategies will look a little different than if we were a tech company trying to maximize our valuation. We are more collaborative, and we have no pride of authorship. We're not trying to create a new tech company, we're trying to create a super valuable tool for society," says Mitchell.

"So while much of this has been built from scratch, it's also true that nothing comes from a vacuum. The newness is an ensemble of approaches that have been honed over time combined with cutting edge tech and applied together in novel fashion. It's soup to nuts—we're not just generating a hypothesis, but scoring and ranking pairings, generating evidence dossiers in seconds for our human experts to evaluate, then proceeding to validate discoveries in wet labs and clinical trials."

Mitchell says for now Every Cure is pursuing three different types of projects. *Frontier Explorers* involve therapeutic candidates that still require additional preclinical work before they can be tested in human clinical trials. *Clinical Gems* focus on medications that are ready for clinical trials. *Unsung Heroes* represent cases where there's a drug already on the market and compelling evidence—maybe patients are taking it off label, or some small trials have indicated its efficacy—that it could be successfully repurposed for another disease.

Last February, Every Cure announced its first unsung hero—leucovorin, a folate analog that could help improve verbal communication in some people with autism spectrum disorder (ASD). The group's algorithms flagged research done over the last two decades showing that a majority of children with ASD have autoantibodies against the folate receptor that helps shuttle vitamin B9 into the brain. "If you give children with ASD leucovorin, it bypasses that blockage and you see increased verbal fluency, faster cognitive processing, and enhanced executive functions," says Mitchell. Leucovorin is commonly used to reduce the toxicity of some chemotherapies, as well as to treat colon cancer and certain types of anemia. Although a few trials of leucovorin have shown positive effects on children with ASD, it is seldom prescribed.

"When pharma companies begin developing a drug, they start with a target of a particular disease area in the human body," Mitchell says. "There might be 20 other diseases that the drug might work for, but they make a strategic and commercial decision to pursue one. The differentiator for us is that we are agnostic as to the disease that we select, and to the drug that can treat it. We're not starting from a disease and saying that we have to cure *this* one—or finding a [particular] drug and working to find a new use for it. This way we get the most out of the 75 million possible pairings between drugs and diseases and let the data guide us to the highest impact opportunities."

"This way we get the most out of the 75 million possible pairings between drugs and diseases and let the data guide us to the highest impact opportunities."

Of course, doctors and their patients *are* fixated on a particular disease and frequently approach Every Cure, as Chen did, looking for a solution to a specific seemingly unsolvable case. "Because we only have limited time and resources, our plan is to help those kinds of researchers and physicians and patients help themselves by releasing some of our tools and capabilities to the public," Mitchell says. "We're hoping to do that by early next year."

Ultimately, Every Cure is looking to launch from five to 10 projects across its three archetypes annually. It's getting ready to launch its first clinical trial this year, according to Fajgenbaum, who adds that they hope to get to the point where the organization is running a few simultaneously at any given time. Every Cure's efforts have recently attracted the attention of the TED Foundation's Audacious Project initiative. Last fall it was selected as one of 10 global nonprofits to receive a five-year, $60 million commitment. The award builds on a $48 million, three-year contract with Advanced Research Projects Agency for Health (ARPA-H), a federal agency that supports biomedical and health initiatives. Those two developments account for about half the funds Every Cure aims to raise to support its AI initiative. "Our AI platform is just a tool to achieve our goals," says Mitchell. "We will happily support and advance any line of investigation that comes from someone else. We will run our own checks, of course, but we want to work together to catalog all the repurposed drugs of the world."

Chen, for example, recently encouraged one of his residents "who has a great idea about Rosai-Dorfman disease [a rare disorder involving an accumulation of a type of white blood cell, primarily in lymph nodes] to send in a proposal about repurposing an existing myeloma drug. We've had some clinical success but want to see what big data shows."

Every Cure believes it will see a lot of opportunity in autoimmune and inflammatory diseases because the immune system is so overlapping and so interconnected. "We're very interested in looking at promiscuous drugs—drugs that work in multiple disease areas and address problems in the body that are known to be important to multiple diseases," says Fajgenbaum. Examples he cites include rituximab, which depletes B cells, a key player in many autoimmune diseases, and tocilizumab, commonly used for treating arthritis.

For more than 10 years now, Fajgenbaum has seen how repurposing common drugs can treat rare diseases and save lives. "I feel so happy thinking of my patients who have thrived after receiving repurposed drugs for Castleman, like Kalia, who started college last September, and Michael, who walked his son down the aisle recently," he says. "But the bigger concept is that we didn't stop with me. That's what I'm most proud of."

JoAnn Greco writes frequently for the *Gazette*.