Nature Biotechnology's academic spinouts of 2017

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Our annual survey highlights how immune-oncology and screens based on the application of cutting-edge omics technologies are providing a launchpad for a succession of startups interrogating biology across biomedicine.

2017 was a good year for biotechs looking to raise money. Venture capital investment in biotech companies reached the stratospheric levels of $16 billion. And it was not only seasoned companies that benefitted—the largesse extended to companies raising their first rounds, which accounted for nearly a third of risk capital entering the sector. An increasing trend toward large tranches of capital going to a few companies was also notable. Indeed, some of the largest series A rounds ever recorded in biotech took place last year.

As in previous years, our survey methodology started by ranking academic R&D-intensive startups according to the amount of early-stage funding they received (a rough measure of investor and commercial excitement in each venture). Our editors then assessed publicly available information about each firm's research to select those that appear in this article. Some firms receiving more funding than those presented here were not included because they were still in 'stealth mode' or declined to be interviewed.

What follows are the stories behind the selected ventures and their technologies. Although our survey is by no means exhaustive, we believe these companies represent some of the best (and most richly financed) science that was commercialized from academia in 2017.

Bill Haney, Tyler Jacks and David Raulet, Dragonfly Therapeutics founders.

Dragonfly Therapeutics: natural killers

Natural killer cells are being turned against tumors with trispecific antibodies. Dragonfly Therapeutics' CEO, Bill Haney, may be the only biotech executive with his own IMDb (Internet Movie database) page. He has directed more than a dozen documentaries on subjects like sugarcane workers in the Dominican Republic and mountaintop coal removal in Appalachia. (He also started an eco-housing business.) In 2015, Haney and his old Harvard College roommate, prominent MIT cancer biologist Tyler Jacks, founded Dragonfly Therapeutics (the company was originally called Equipoise Therapeutics) with prominent natural killer (NK) cell researcher David Raulet, of the University of California, Berkeley. Raulet, faculty director of the university's Immunotherapeutics and Vaccine Research Initiative, has been studying NK cells for almost 30 years.

Several companies have seized on NK cells, lymphoid cells of the innate immune system, for cancer immunotherapy[1]. NK cells, unlike T cells, do not need to recognize antigen presented on major histocompatibility complex (MHC) class I molecules. They circulate primed and ready to kill. Paradoxically, they identify prey mainly by looking for the *absence* of MHC class I on neighboring cells, along with the presence of stress ligands, which bind and trigger a variety of activating receptors on the NK cell surface. (A balance of signals from inhibitory and activating receptors can be tipped in either direction.) Although NK cells can kill tumor cells and play a role in antitumor immune surveillance, they are unable to eradicate established human tumors by themselves, even though such tumors often downregulate MHC class I molecules, making the tumors in theory vulnerable to NK cell attack.

So Dragonfly, based in Cambridge, Massachusetts, is developing trispecific antibodies to amplify NK cell antitumor immunity by bringing these cells into direct contact with tumors. The company's trispecifics (called TriNKETs) target an undisclosed tumor antigen with one arm, while the other two arms

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engage activating receptors on the NK cell. Dragonfly's interest in NK cells was "in part driven by six years of research in Tyler's lab, demonstrating that they can kill cancer cells powerfully and directly," says Haney. "And they can amplify the performance of T cells and B cells, turning cold tumors 'hot'. And they do so with a unique safety window that suggests they'll be far less toxic than classic T-cell therapies."

The safety window is based on the display by normal cells of MHC class I, which binds to inhibitory receptors on NK cells called KIRs (killer cell immunoglobulin-like receptors). This binding normally prevents NK-cell-mediated autoimmunity. But the safety window is not absolute, says Martin Felices, a University of Minnesota (Minneapolis) immunologist, whose group is also working on NK cell-activating trispecifics together with GT Biopharma in Los Angeles. With Felices' molecules, called TriKEs, or with Dragonfly's TriNKETs, "you're pushing the activation signal beyond what it would be normally," says Felices. "So you're shifting the balance towards activation." That's necessary to kill tumors, he adds, but runs the risk of overriding the negative signals through KIRs that keep NK cells from attacking normal cells. So Felices expects some side effects.

Efficacy can't be taken for granted, either. "NK cell immunotherapy is going to be limited by the number of NK cells that are present, and how functional they are," says Felices. Also, evidence from Raulet's laboratory, among others, shows that NK cells, counterintuitively, can be put into a state of anergy, or hyporesponsiveness, after encountering tumors lacking MHC class I molecules[2].

Another mechanism of tumor cell immune evasion is the shedding of soluble ligands to the NK-cell-activating receptor NKG2D. The disappearance of these ligands from the tumor cell surface makes them less visible, and the shed ligands can desensitize the NK cells, though Raulet's group has shown that, unexpectedly, certain ligands can activate NKG2D and improve tumor killing in this context[3]. Recently, Raulet showed that NK cell exposure to activating receptor ligands, superinduced on normal cells in cancer models, can directly desensitize the NK cells and impair tumor killing[4].

Dragonfly is relying on Raulet's advice to help navigate these paradoxes and complexities. "We're the beneficiaries of his post-publication thinking," says Haney. Dragonfly's CSO, Nicolai Wagtmann, has similar expertise along with extensive industry experience. Wagtmann, in 1995, co-discovered KIRs, and he later worked as vice president and head of inflammation biology at Novo Nordisk (Bagsvaerd, Denmark), later becoming CSO at Innate Pharma (Marseille, France).

Innate Pharma is the leading NK cell immunotherapy company, but its stock price fell almost 70% last year owing to clinical trial setbacks for its anti-KIR antibody, lirilumab. Haney declines to comment on possible reasons for the failure, but says his own company's NK cell expertise sets it apart. "We don't know of any examples where…what we believe to be [the] right receptors in the right combinations and in the right way were targeted," he says. Dragonfly boasts Nobel Prize winner and former US National Institutes of Health director Harold Varmus, co-discoverer with J. Michael Bishop of the first proto-oncogenes, and Patrick Hwu, division head of the cancer medicine department at the MD Anderson Cancer Center (Houston), on its scientific advisory board.

Dragonfly is also well-funded. A strategic collaboration with Celgene (Summit, New Jersey) yielded $33 million in upfront payments in addition to future milestones and royalties. (Celgene can license up to four clinical candidates.) Haney expects the company's first molecule to enter the clinic sometime next year. Dragonfly's founders seeded the company without venture capital, instead drawing on personal funds as well as family offices, with investors like Tim Disney, great-nephew of Walt Disney (and Haney's moviemaking partner), and Sean Reilly, CEO of Lamar Advertising Company (Baton Rouge, LA, USA).

Despite his CEO duties, Haney still spends much time working behind the camera. His latest filmmaking project is a documentary about MD Anderson immunologist Jim Allison, who pioneered checkpoint blockade immunotherapy for cancer, despite widespread skepticism. "Jim persevered," Haney says. "He really understood what he was talking about… . I'm not one of them, but one thing Dragonfly is absolutely doing is enlisting great scientists." *KG*

Vividion: binding the proteome footprint

Chemical probes designed with single amino acid specificities enable the screening of thousands of sites across the human proteome. For more than a decade, Ben Cravatt has been among the leaders of the field of chemical proteomics—a field devoted to the application of small-molecule probes to interrogate human proteome function. Work out of Cravatt's laboratory has already launched two companies in the San Diego area—ActivX (a wholly owned subsidiary of Tokyo-based Kyorin Pharmaceuticals) and Abide Therapeutics. 2017 made it three, with his latest launch, Vividion. The company started out with one person soldiering away in the bowels of the Scripps Research Institute in La Jolla, California, where Cravatt has been since the mid- 90's 1996 when he came to do graduate studies. As Vividion's CEO Diego Miralles describes it, "A year ago, when we had an A round [of funding], we literally came out of the basement into the light of the world." Cravatt with his Scripps colleagues Phil Baran and Jin-Quan Yu launched Vividion in February 2017 with a $50-million A round from Arch Venture Partners (Chicago), Versant Ventures (San Francisco) and Cardinal Partners (Princeton, NJ, USA).

Ben Cravatt, Vividion co-founder

Phil Baron, Vividion co-founder

Jin-Quan Yu, Vividion co-founder

Cravatt points to a set of technical advances over the past decade that served as the springboard for their work—the unearthing of thousands of disease-related proteins with the explosion of information coming from genome sequencing, and developments in high-resolution mass spectrometry (MS), which can now distinguish among thousands of protein species. With these tools at their disposal, researchers can determine precisely how many proteins and protein variants there are in the proteome, and most importantly, the fraction of the proteome that remains without functional characterization. "We're now in a very privileged position—those of us interested in function assignment for drug development no longer have to rely on a mouse or yeast or worm to select targets. We can now use human genetic information to point us to the proteins of greatest relevance to disease," says Cravatt.

The first iteration of Cravatt's commercial work on chemical proteomics focused on developing chemical probes for cataloging enzyme classes. But these chemicals can do more than that. "Such probes not only provide a handle for identifying proteins within a class, they can provide information on druggability, as the probes read out the functions of enzymes in their native state," he says.

In the run-up to Vividion, Cravatt's team moved beyond enzyme-class-restricted probes to designing probes with single amino acid specificities, thus expanding profiling capability from hundreds to thousands of sites across the human proteome. By broadly targeting cysteines or lysines, the amino acids that Cravatt has thus far probed, and making use of high-resolution MS technology, they are able to inventory thousands of targetable sites in parallel, liberating researchers from having to come up with target-specific assays for proteins of interest. "You can now imagine doing fragment-based drug discovery across the entire proteome in parallel in a native system, where all the interactions that proteins engage in, all the modifications are intact," he says. And, of course, the brass ring will be identifying druggable sites on what have been, up until now, undruggable proteins, despite there being, in some cases, a rich understanding of their roles in biology and disease.

Matthew Bogyo, a chemical biologist at Stanford and longtime collaborator of Cravatt's, says this is where Cravatt's strategy adds "real benefit" and is different from what is typically done (i.e., focusing on specific targets where there is existing information and targeting known sites within those protein targets). "Here is a shotgun approach—you have a molecule you think is interesting and has an interesting phenotype, now you can find what it binds and that includes targets that might not be binding through a defined active site or substrate binding pocket," he says.

What all three of Cravatt's companies have in common that differentiates them from traditional drug discovery programs is the ability to perform drug development in native biological systems, focusing on the most exciting proteins in human biology that have resisted classic approaches and, of course, applying this platform in a way that allows the discovery of ligands against those undruggable proteins that can then be advanced toward clinical development. To do this requires striking a balance between reactivity and specificity in interrogating a broad functional subset of the proteome.

In addition, the platform can be used to identify sites of ligand binding in the proteome that aren't actively involved with enzyme activity, but that are allosteric or involve protein–protein interactions. "This significantly expands the way we think about small molecules and provides a ligand-centric, proteome-wide drug discovery approach," Cravatt says. It's even possible to adapt silent sites for drug development by, for example, tagging proteins for degradation. This is being done in other ways in several other companies, but a major gatekeeping requirement is the discovery of small-molecule ligands for particular proteins of interest, and here is where Cravatt feels Vividion is uniquely poised to contribute. "It's about finding ligands and [sites that bind ligands] throughout the proteome, which you can determine if they have a direct functional impact, or an allosteric effect, or if they can be used to tag the protein," says Miralles.

In his 2017 paper in *Nature Chemistry*, Cravatt's academic group described an amine-reactive probe that provided access to over 9,000 lysines in the human proteome, and showed that most of the liganded lysines resided on proteins not in DrugBank, meaning there are no previously described small-molecule probes for many of these proteins[5]. Furthermore, they showed that the probes knocked out some *in vivo* activities when bound to highly reactive lysines; the catalytic activity of several enzymes was inhibited by ligand binding either to active sites or to allosteric sites. Interestingly, the probe disrupted protein–protein interactions in a transcriptional regulatory complex SIN3A–TGIF. This particular complex has been associated with invasiveness of triple-negative breast cancer, thus providing a potential new target for a difficult-to-treat cancer.

Bogyo is a "big fan" of approaches like these that go outside conventional practice. "A lot of drug discovery has a very set mindset about how you go about picking a target and validating it and doing your screen, and so on. Clearly, the pipeline in drug discovery could use a larger pool of things entering. These kinds of strategies are really good—to kind of shake things up and make pharma think about different ways of screening."

Moving Vividion on to other amino acids seems unnecessary, as targeting just these two amino acids, Cravatt feels, will keep Vividion busy for quite a while. "It's not an overstatement to say that any protein in the proteome can be assayed for druggability in a native biological system. I don't think there's a region of the proteome outside these platforms," he adds. Cravatt sees the potential to work in multiple therapeutic areas, which could be narrowed slightly with their first partnership. In March, Vividion announced a $101-million (upfront cash and equity collaboration) partnership with Celgene for drug discovery in cancer, inflammation and neurodegenerative diseases.

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Enterin: circling the gut–brain axis

What to do when the gut–brain dialog is interrupted. Some of the most intractable diseases known to man are neurological conditions. These conditions have confounded efforts to treat them. They challenge our ability to model them in animals. And studying brain disease in patients has also proven difficult. The litany of clinical failures in Alzheimer's disease alone is testament to the difficulty of addressing these complex disorders.

Denise Barbut, co-founder Enterin

The need for new approaches to addressing neurological disease is one reason why progress in understanding gut–brain biology is attracting interest. This relatively new field looks at the signals sent to the brain from the gut via the enteric nervous system (ENS). As the impact of the gut on many aspects of human health has become increasingly appreciated, interest in the gut and its microbiome has ramped up. But now, a small cadre of companies has been formed around the idea of using the gut's nervous system to tackle diseases, including those of the brain.

One such company is Philadelphia-based Enterin, co-founded in 2016 by Michael Zasloff, a professor of surgery and pediatrics at Georgetown University School of Medicine (Washington, DC) and a pioneer of this field. Enterin is focused on restoring signaling between the gut and the brain. Their first target is Parkinson's disease (PD). Many patients with PD display gastrointestinal (GI) symptoms even before the onset of more commonly known neurological ones. The hope is that by treating the condition through the gut, progression can be stopped early on. Furthermore, this approach could potentially avoid safety risks associated with drug delivery to the brain.

Somewhat improvidently, Enterin's roots go back to observations made by Zasloff in the 1990s on the healing properties of molecules that occur naturally in frogs and sharks, which he was investigating for their potential as broad-spectrum antivirals. One such molecule found in tissues of the dogfish shark, squalamine, was particularly intriguing, as he found that it disrupted the aggregation of α-synuclein on membranes[6].

α-synuclein tangles in the brain are a hallmark of PD and other neurological disorders. Furthermore, a synthetic analog of squalamine, with both antiviral and anticancer properties, had already been tested in human trials for cancer and eye conditions, providing further confidence that the molecule is a good drug candidate because it has a known safety profile.

Normally, α-synuclein facilitates the flow of chemical signals along nerves. But when too much of the protein is produced, it clumps,

Michael Zasloff, Enterin co-founder

and those aggregates disrupt cellular homeostasis and communication. They can also travel along nerves all the way to the brain, where they cause neuronal death. The process is complex, but according to Enterin co-founder, CEO and chief medical officer Denise Barbut, α-synuclein that accumulates in the brain stem, can jump across to nearby brain regions. The clumps eventually reach the substantia nigra, where dopamine is produced. "They damage that part of the brain as well as the dopamine-carrying neurons that go from the substantia nigra to the basal ganglia. As dopamine input to basal ganglia falls, movement disorders begin," she explains.

Animal studies suggest that microbes in the GI tract can induce toxic α-synuclein aggregation in the ENS. Phospholipid binding, occurring as the protein attaches to cell membranes, has also been shown to accelerate α-synuclein aggregation. As a result, Zasloff and colleagues decided to investigate whether compounds that can displace the protein from the membrane could interrupt that toxic process. They found evidence that it does.

For example, in *Caenorhabditis elegans* engineered to produce human α-synuclein, Zasloff and his group showed that indeed, squalamine can displace α-synuclein, interrupt clumping and restore normal membrane activity. The worms, which are paralyzed, become mobile again[7]. Furthermore, in a mouse model of PD the drug can reverse constipation. "The compound works in the gut, not the brain," Zasloff points out. In the gut, α-synuclein is believed to act by improving motility directly. But interrupting the clumping of mutated α-synuclein should also protect the brain. This approach, safer and easier to study than something that works directly on the brain, led to the development of Ent-01, a synthetic derivative of squalamine.

"We think there are going to be several benefits of Ent-01," Zasloff says. "Not only will it reverse gut problems, such as constipation, but it will then allow signals that were blocked to be sent to the brain." The compound is currently being tested in a 50-patient phase 1/2a clinical trial (RASMET) in patients with a PD diagnosis who are also experiencing constipation. The trial endpoints are safety, tolerability, pharmacokinetics and pharmacodynamics of ENT-01 to relieve PD-associated constipation. The study will also collect data about central nervous system symptoms, including sleep, random eye movement (REM)-behavior disorder, depression, fatigue and motor symptoms.

Zasloff believes the gut–brain axis may also play an important role in other neurologic conditions, including autism and schizophrenia, both of which also can include constipation as a symptom. "Wherever you have a disruption of signals being sent from the gut to the brain, this may be a useful approach," he says. He adds that, "If you have a disease where the symptoms include things such as change in mood or sleep patterns, it's possible that the problem is a gut–brain interaction." The company has also been gathering data about hallucinations in their PD trial, and they are planning trials of ENT-1, or related compounds, for hallucinations in Parkinson's, autism and schizophrenia, according to Barbut.

Zasloff launched Enterin in a partnership with Barbut, using their own funds and support from an angel investor. In July 2017, the company raised $12.7 million in a series A financing round, which included investment from New Ventures III (New Providence, NJ, USA). According to Barbut, Enterin is seeking additional funding to move ENT-01 into phase 2b for Parkinson's, as well as into other indications.

John Cryan, head of anatomy and neuroscience at University College Cork (Ireland) points out that Enterin is basing their whole model on the concept of α-synuclein spreading from the gut to the brain. "That's something that is gaining a lot of attention, from being an out-there some 15–20 years ago." This is thanks to epidemiology coming out of Scandinavia in the last few years that showed that people who have had their vagus nerve cut (old treatment for peptic ulcers) have reduced incidence of Parkinson's[8]. "With this epidemiology, they really could be onto something," Cryan says. *MAB*

BlueRock Therapeutics: iPSCs for regenerative medicine

Reprogramming cells to create therapies for Parkinson's disease and heart failure is the raison d'être of one of the most well-capitalized startups in biotech history. In early 2016, Axel Bouchon, head of Bayer's Leaps by Bayer innovation program, approached the life sciences investment firm Versant Ventures (San Francisco) about starting a regenerative medicine cell therapy company. Versant was already thinking along those lines. Despite a long history of failure for companies in that space, "technology has matured," says Jerel Davis, a Versant managing director, "lending itself to more translatable science and therapeutics." By year's end, BlueRock Therapeutics was launched, with four well-known scientific co-founders and with $225 million—one of the largest series A rounds in biotech history.

Lorenz Studer, BlueRock founder

BlueRock, based in Cambridge, Massachusetts, will be transplanting allogeneic cells derived from induced pluripotent stem cells (iPSCs), an unproven cell source. (Worldwide, only a few patients have been treated to date with such cells.) "The technologies to grow them, to analyze them, to differentiate them have radically improved," says BlueRock CEO Emile Nuwaysir. BlueRock's first clinical application will be dopaminergic neuron transplantation for Parkinson's disease (PD), followed by cardiomyocytes for myocardial infarction (MI) and heart failure.

BlueRock co-founder Lorenz Studer, a neuroscientist at the Memorial Sloan Kettering Cancer Center (New York), developed the now-standard protocol for differentiating pluripotent cells into dopaminergic neurons[9], and has spent five years preparing a clinical trial using human embryonic stem cells (hESC). BlueRock is sponsoring that trial, to begin later this year, but the eventual commercial product will be derived from human iPSCs, says Nuwaysir. Such cells are easier to characterize and standardize from starting material. But why allogeneic lines instead of autologous, when iPSCs are by definition matched to patients? Autologous cells can't be made into a standardized product, and they shouldn't be necessary for Parkinson's, Nuwaysir says, because of the partially immune-privileged nature of the brain.

Cell therapy for Parkinson's has a three-decade history, showing mixed results. In Parkinson's, the dopamine-producing cells of the substantia nigra gradually die, leading to loss of movement, rigidity and tremor. In 1987, neuroscientists and surgeons at Lund University in Sweden began transplanting cells from the substantia nigra of brain tissue obtained from aborted fetuses into the striatum of Parkinson's patients. (Cells grafted into the substantia nigra do not work, because they cannot grow their axons long enough to reach the striatum, where dopamine is released.) Over 200 patients were eventually treated worldwide. A few showed definite improvement, and post-mortem exams of patients who died of unrelated causes showed long-term graft survival, massive innervation and synapse formation. But two randomized trials, reported in 2001 and 2003, showed no significant improvement over placebo, and many patients developed dyskinesias—involuntary writhing movements

Michael Laflamme, BlueRock founder

of the arms, legs or head. These studies effectively killed cell transplantation for PD.

But with the maturing of hESC and iPSC technology, "there's a new emerging interest," says Clive Svendsen, a stem cell scientist at Cedars-Sinai Medical Center (Los Angeles). Besides BlueRock's trial, at least three others could begin this year or next. "The advantage of iPS or embryonic stem cells is you have a reliable source of tissue to do the differentiation," says Svendsen. "You don't have to rely on fetal tissue…which causes a lot of variation." Nuwaysir stresses that BlueRock will be making cells to a uniform standard that meets good manufacturing practice (GMP). Fetal transplants, he says, showed that "cell therapy can work, if we just had the right cells, under industrial manufacturing control, productized. And I think that's where we are today."

But BlueRock's Parkinson's treatment must overcome some hurdles. For example, the field has struggled to find the right degree of neuron differentiation for transplantation. Put neurons into the patient at too early a stage, and they don't become fully functional, owing to the lack of developmental cues in the adult brain. Wait too long and the axons rip from the cell body when it's removed from the culture dish, leading to cell death. "There's a sweet spot in the middle where it's going to be perfect timing to put the cells into the patient," says Svendsen. "A lot of groups are getting close." Nuwaysir says he's confident in Studer's differentiation protocol.

And the safety of iPSC-derived cells remains in question. Cells can acquire mutations and epigenetic or chromosomal changes during reprogramming, with tumorigenesis (or other problems) a theoretical possibility. "These are all straightforward to test, there are ways to do it, and we look forward to doing it as rigorously and safely as possible," says Nuwaysir.

Gordon Keller, BlueRock founder

Nuwaysir avoids the term "cure" when it comes to PD. The disease is complex, involving cells other than dopaminergic neurons. "Our intent is with a single intervention to provide a durable, meaningful benefit to the patient," Nuwaysir says. Svendsen says BlueRock's trial timing is appropriate. "It needs to be done," he says. "So long as it's posed and it's pitched in the right way, that this is a new treatment, not a cure for Parkinson's, then I'm all for it." Svendsen is working on transplanting fetal-derived astrocytes engineered to produce glial-cell-derived neurotrophic factor (GDNF), an approach he considers complementary to BlueRock's. Nuwaysir declines to predict when BlueRock will launch its first PD trial using iPSC-derived neurons.

BlueRock's second program, cardiomyocytes for heart failure, lags behind the PD program. As with dopaminergic neurons, the cardiomyocyte field has struggled to find the right differentiation protocol. Nuwaysir says BlueRock co-founders Gordon Keller and Mike Laflamme, pioneers in the field (both at University Health Network in Toronto), can now make pure populations of mature functional ventricular cardiomyocytes. "It's really at this point a process-science challenge to make sure you can make enough of them in a quality way, and we're very well along in that," he says.

But a major hurdle is arrhythmias. Two recent monkey trials showed extensive cell engraftment and cardiac remuscularization using transplanted ESC- and iPSC-derived cardiomyocytes, respectively[10,11]. Yet in both trials, animals developed non-lethal ventricular arrhythmias. "That is the primary safety concern that you need to prove that you can avoid and manage," says Nuwaysir. "We think we can do that." The specifics, he says, are proprietary.

Versant and Bayer knew the challenges when they launched BlueRock, and funded it for a three- or four-year initial runway. Davis acknowledges the failures of previous regenerative medicine companies, but says BlueRock is different. "As with all cycles of investment, if you invest too early…the science may not be ripe enough," he says. "If you invest too late, you may miss the opportunity. So our goal as investors is to try to hit the wave when it crests…. We believe that's what we're doing here." *KG*

GigaGen: fast-tracking antibody discovery

Rapid mining of the natural human B-cell repertoire is unearthing rare and effective binders. Since the invention of hybridoma technology, monoclonal antibodies (mAbs) have now become a mainstay of drug development, representing an ever-increasing proportion of biologic approvals every year. However, the technology remains painstakingly slow and expensive, and clinical successes notwithstanding, hybridomas sample only a tiny fraction of the millions of antibodies that comprise a human antibody repertoire. With the advent of quick and relatively inexpensive high-throughput sequencing platforms, researchers have a new discovery tool, and GigaGen is among the first to connect direct sequencing with antibody drug discovery. Its Surge technology combines microfluidics with high-throughput genomics and protein library screening to pull out rare, high-affinity antibodies. "We built our technology specifically for drug discovery and development," says GigaGen co-founder and CEO Dave Johnson.

Dave Johnson, GigaGen co-founder

Everett Meyer, GigaGen co-founder

The S. San Francisco-based GigaGen spent six years working in relative obscurity. Johnson, a genomics expert and co-founder of prenatal testing company Natera (San Carlos, CA, USA), and his friend from grad school, Stanford immunologist Everett Meyer, felt that immunology was lagging behind in the genomics revolution and decided to combine their areas of expertise to try to change that. And so, in 2010, began GigaGen. The issue, as the two friends saw it, was that the technologies commonly in use by immunologists at the time failed to provide much insight into the immune system. "They usually are low-throughput methods, just giving [a] fraction of the information that you need to understand immune cells' repertoires," says Johnson. What GigaGen has assembled allows screening of an entire antibody repertoire in combination with functional assays, so that in the end, there is not just a collection of sequences, but a collection of antibodies that work.

Surge does this by generating single-chain variable fragment (scFv) libraries representative of the native antibody repertoire from complex mixtures of B cells. B cells are isolated as single cells in microdrops, where heavy- and light-chain antibody genes are amplified and physically linked. These constructs are then put directly into expression systems (yeast or mammalian cells), displayed on the surface and screened in functional assays. High-affinity binders can be isolated by fluorescence-activated cell sorting (FACS) of the scFv on the surface of yeast, or the antibodies can be expressed in Chinese Hamster ovary (CHO) cells for other kinds of antibody characteriza-

tion—epitope binding, cellular activity assays, affinity.

In the first airing of the technology, in a set of papers that came out in the fall of 2017, GigaGen researchers described the discovery of high-affinity human antibodies against influenza A and *pneumococcus*[12,13]. Starting with peripheral blood from both immunized and non-immunized human subjects, they isolated 247 natively paired anti-pathogen scFvs and showed that all antibodies tested bound the appropriate antigen and the majority of those tested neutralized viruses or worked in cell-killing assays (100% of influenza antibodies and 70% of pneumococcus). This is GigaGen's strong suit, according to Johnson: isolating natural scFv cognate antibodies from more than a million single cells and screening for binders. Whereas others have sequenced antibody repertoires of millions of cells, Johnson claims that there is no way to turn all of those antibodies into protein for testing without spending a lot of time and money. "There is no reliable method to know which antibodies are the ones you want from the sequences alone," he says. "So folks that just do sequencing have to make guesses that are almost always wrong."

2017 was big year for GigaGen—not only did they publish their first set of experiments, but they announced a deal worth $50 million ($35 million for a stake in the company and $15 million in licensing fees) with the plasma-derived therapy company Grifols (Barcelona). Up until then, the company was run on an impressive amount of federal funding—over $10 million in Small Business Innovation Research (SBIR) grants, from over 100 applications (not all of them successful). With its investment in GigaGen, Grifols is getting a 44% stake in the company, providing GigaGen with the means to take through to market what will certainly be their first product (recombinant polyclonal antibody for people with immune deficiencies) but also with the freedom and capital to work on their own drug discovery programs. By eschewing venture capital in the company's early days, Johnson says that they retained complete control of the company. "We were able to follow our own adventure, as it were," he says. He also feels that going the grant route may have allowed them greater freedom to innovate. "When you think about venture capital, it's fewer than 50 people in the country making decisions on where money goes and which innovations get done. Whereas SBIRs is a much larger group and you can do more innovative things through grants than you can often through venture capital," he says.

GigaGen has two main focus areas: immune deficiencies, partnered with Grifols, and immune-oncology, where the discovery of targets is outpacing the ability to develop therapies. A polyclonal antibody program partnered with Grifols is already at the manufacturing stage, and working toward an investigational new drug application (IND), expected to be filed next year. George Georgiou, of the University of Texas at Austin, who has worked both with polyclonal antibodies as well as screening technologies for isolating natively paired antibodies, finds the polyclonal program intriguing. "You may have thousands of B cells that have antibody specific to the target, but only very few antibodies that are selected by the immune system produce sufficient amounts to constitute the serum polyclonal repertoire," he says.

With oncology, Johnson says, "We figured out is that strategically it makes a lot of sense to use our technology because it's really fast." After receiving their financing from Grifols in July, they chose 17 immuno-oncology targets: some new, some already in the clinic. In five months, they had identified 2,300 antibodies that have high affinity against the targets. "That's competitive with any big pharma large hybridoma programs; we're competing at the same level with a staff of 11," he says. The staff currently stands at 14.

Sai Reddy, who works on antibody repertoires and diversity at ETH Zurich, thinks GigaGen is in effect outsourcing almost all the antibody engineering step in the human or mouse by being able to interrogate the large diversity present in the human or mouse repertoire. "If you were to isolate antibodies by hybridoma screening or recombinant libraries, you then would almost always have to do some additional engineering." By combining screening with sequencing, GigaGen gets a large number of variants out of their platform, allowing them to select those antibodies with the functions they want. Johnson would agree. "What sets us apart is the volume of rare binders that we capture. Since our efficiency is leaps and bounds beyond hybridoma or phage display capture, we capture lots of rare binders versus just a few, eliminating the need [for] iterative discovery. We get it all in one shot," he says. *LD*

LifeMine: moving up the evolutionary tree

Genomics is enabling natural product discovery and development from fungi. Microbes have been mined for natural products with healing properties for literally centuries. However, the last natural product antibiotic to reach the market is now something like 30 years old. Into this space has stepped Greg Verdine, professor of chemistry at Harvard and serial entrepreneur, with two of his recent biotech startups: Warp Drive Bio (Cambridge, MA, USA), launched in 2012 to mine natural products from bacteria[14] and his latest, LifeMine Therapeutics, which has turned to fungi.

Greg Verdine, LifeMine Therapeutics founder

LifeMine launched in September 2017 with a $55-million series A round from a stellar group of investors, including Verdine himself, who is venture partner at WuXi Healthcare Ventures (Cambridge, MA, USA, and Shanghai, China). Also in the mix are Foresite Capital (San Francisco), GV (Mountain View, CA, USA), Arch Ventures, Boyu Capital (Hong Kong), Blue Pool Capital (Hong Kong), MRL Ventures Fund (Cambridge, MA, USA) and Alexandria Venture Investments (Cambridge, MA, USA). Verdine says his motivation for starting these companies derives from his frustration that a large portion of human biology is undruggable. "It drove me crazy that there was this disconnect between biology, knowing what the right targets are, and yet 80% of the time the chemists or people who make mAbs would say, 'No that's not actionable.'"

Verdine argues that high-throughput genomics and bioinformatics have resurrected the quiescent, if not moribund, field of natural product discovery. According to him, "It's really only in the last decade or so that people have begun to focus in any significant way on the architecture of secondary metabolite genes in fungi, coincident with the availability of whole genome sequencing." He cites two reasons for this. Trying to fish out metabolites from extracts of microbes is a messy and inefficient process. The organisms produce a plethora of molecules with confounding activities; using biological activity to guide discovery of these molecules can lead nowhere. And second, the pathways tend to be tightly regulated and hence the metabolites may be produced only under very specific conditions. "Searching through metabolite space will often yield nothing," says Verdine.

That's where the genomics comes in, with a little help from Mother Nature. In fungi, biosynthetic genes tend to be organized in clusters, as in bacteria, which makes discovery easier. "If you are doing some kind of a search for gene[s] that make a natural product, once you land in a cluster, just by proximity, you have everything that is required to make the product, whether you understand all the details of biosynthesis or not," says Verdine.

Verdine finds fungi alluring because of

their position on the tree of life. He calls them "tweeners," as they interact with organisms both above and below them in the evolutionary stratosphere, through producing secondary metabolites that foster their own growth and survival. With bacteria, the targets tend to be other bacteria, which is why, as a group, they have been a rich source of antibiotics. But with fungi, you are more likely to find molecules that act on eukaryotic targets. "Those molecules frequently have been evolved to target other eukaryotes but cross over to humans because humans are so closely related to the real evolutionarily targeted protein," he says.

The trick is to identify clusters that are useful, and here's where LifeMine's 'secret sauce' comes in. Starting with genome sequences, of which there are roughly a thousand in public databases already, they cull out the biosynthetic gene clusters from the framework genome, creating, what Verdine calls, a 'clusterome' of sorts, which they then sift through to find molecules that might have certain functional roles. Without disclosing the specifics of how they do that, Verdine says that if you analyze the organization, composition and sequence of these biosynthetic gene clusters carefully enough, you can begin to develop hypotheses for which molecules are encoded by them, what those molecules actually do. "It's not perfect," he says, "but at least it restricts the universe down to a size that you can actually try—that you can clone, that you can produce, that you can then test."

Cloning large gene clusters used to be a huge problem but is another area in which strides have recently been made. Making clusters of 50 kb and larger and putting them into heterologous organisms is doable now. What is still challenging is getting transcriptional activation to work. Another enabling advance is the development of synthetic biology approaches that allow targeted overexpression of clusters in heterologous hosts. LifeMine is developing the ability to make focal changes in the fungal biosynthetic machinery to predictably alter the structure of the encoded molecule, something that's been done in bacteria, but not yet established for fungi, because the biosynthetic code is much more complex, according to Verdine. "This is like the dream of the field—synthetic chemist would be able to dial up a derivative that would give them an entry point for modification and the synthetic biologist would make that derivative and then hand it off to the chemist." Verdine envisions developing the same capability in yeast.

Stanford bioengineer Michael Fischbach, who works on natural products from microbes, is a believer in the approach. "Looking for molecules is important," he says. But he adds the real need is to find better ways to go from clusterome to drugs, involving clever and scalable microbiology, synthetic biology or genetics to lay hands on small-molecule products, do deep domain-specific biology to figure out what each molecule does and then turn it into a drug. "There has been a mistaken assumption that if we just find more natural products, the rest of the process will work itself out and drugs will magically appear. It's not that I think we shouldn't be looking for more molecules; we definitely should. But equal attention and creativity need to be paid to the downstream steps on the critical path from cluster to drug," says Fischbach.

Verdine is excited to be taking the helm of the company. In 2012, he took a two-year sabbatical from Harvard University to run Warp Drive. "It began my own personal growth, to learn how to be an actual CEO, and run a company with a proper board of directors," he says. Harvard is allowing Verdine to retain his position at the university for three years while he heads LifeMine and Fog Pharma (Cambridge, MA, USA), a stapled peptide company he formed in 2016. This is the first time they have allowed such an arrangement, and he is grateful for the opportunity. "I started my career at Harvard and I want to end it there," he says.*ID*

Repare Therapeutics, Tango and EdiGene

Angel Sfeir, Repare cofounder

CRISPR-based screens provide a new approach for attacking cancer with synthetic lethals. CRISPR gene editing technology has been widely heralded as a powerful new therapeutic modality for correcting genetic disease. Now companies are hoping to employ the CRISPR endonuclease system to galvanize efforts to discover synthetic lethal genes—believed to be an Achilles' heel of cancer cell genomes. Three startups employing this approach that have raised sizeable series A rounds recently are Repare Therapeutics of Cambridge, Massachusetts and Montreal, Tango Therapeutics of Cambridge, Massachusetts and EdiGene of Beijing.

Synthetic lethality is one of those concepts that seem so elegant it can't fail. Many cancer cells are already hobbled by mutations affecting their ability to repair their DNA, why not take advantage of that to deliver a fatal blow by targeting back-up repair mechanisms? The idea is that a gene defect in combination with other defects can cause cell killing, whereas alone, it will not. In a now classic example, cells harboring *BRCA* mutations with reduced ability to repair DNA can be killed by inhibiting a secondary DNA repair mechanism, poly (ADP-ribose) polymerase (PARP). Several PARP inhibitors have now received FDA approval.

Until recently, however, the tools available for creating synthetic lethal screens have been less than perfect. Gene knockdown technology, such as small-interfering RNA (siRNA) or short hairpin RNA (shRNA), have already been widely employed to create synthetic lethals. But the problem is that "these tools suffered from their high false-detection rate—false negatives and false positives— as well as dependence on gene expression levels," explains Kim Seth, Repare Therapeutics' head of business and corporate development. "Getting good hits was like finding a needle in a haystack. It was not a very productive endeavor," he says. Lots of false hits translated to lots of blind alleys and wasted time and money.

CRISPR endonuclease screens provide a solution to these problems. "We have much better signal to noise with lower false-detection rates with our top hits tending to hold up much better under validation," adds Seth. With the new CRISPR-based tools, researchers can do genome-wide screens in an unbiased way. "We are finding targets we may not have known to look for, but they hold up under validation," he claims. "That is the benefit of this platform."

The Repare platform is based on technologies from the company's three scientific founders: Daniel Durocher and Frank Sicheri both at the Lunenfeld–Tanenbaum Research Institute in Toronto, and Agnel Sfeir at the New York University (NYU) Langone Medical Center. Durocher pioneered using CRISPR for synthetic lethal screening[15]. Repare's platform starts with creating a set of isogenic cell lines, differing by one genetic alteration that represents mutations found in patients with serious cancers. A CRISPR–Cas genome-wide screen, with a proprietary set of gRNAs, is used to identify other genes, which, when knocked down, are synthetic lethal with the original mutation. Sicheri, meanwhile, is a structural biologist and X-ray crystallographer, who is helping to enable structure-guided drug discovery.

The idea is to create a platform that will generate a pipeline of candidate drugs. But thanks to Sfeir's work at NYU on genome instability and polymerase θ (Polθ), the company already has its first drug in development—a small-molecule inhibitor of Polθ. Polθ appears to play an important role in repairing DNA double-strand breaks (DSBs), when the more typical

repair activities, homologous recombination (HR) and classic non-homologous end-joining (C-NHEJ), are inactive. Termed alternative-NHEJ, Polθ activity is suppressed in healthy cells, but is overexpressed in many tumor types and associated with poor clinical outcomes in both ovarian and breast cancers. These findings have made this pathway become a hot target.

Sfeir had been working on DNA repair of telomeres, and after finding that inhibiting Polθ can prevent the fusion of telomeres, which can appear as DSBs when unprotected, she decided to try it on breast cancer cells. She found that knocking out Polθ killed cancer cells, presumably due to the absence of both HR and alternative-NHEJ[16].

Sfeir expects that Polθ inhibitors will perform in the clinic better than PARP inhibitors, based on several features including tissue distribution. Side effects that patients on PARP inhibitors are suffering from are unlikely to be seen with Polθ.

Although Polθ is a promising first target, Repare plans to spread its net wider, focusing on genome instability in cancer. According to Durocher, more than just repair enzymes are involved in maintaining genomes. Cell-cycle problems affect genome stability, for example, as can chromatin-modifying mutations. "We're really going from the perspective that genome maintenance processes are essential and they are also partially disabled in tumors, which provides promising targets across multiple cell types." They already have two other potential programs, for undisclosed targets, in the wings. "We are generating high-resolution crystal structures and co-structures across our portfolio, not just around Polθ," says Seth. The goal is to reach the clinic with their first small-molecule inhibitor of a synthetic lethal target for cancer by late 2019/early 2020.

The company was nurtured for more than a year and a half by Versant Ventures, which brought the group together, as both Sfeir and Durocher describe it. "VCs [venture capitalists] were talking to the NYU office, and they came to me with the idea of starting a company around Pol-θ inhibition. At the same time, the same VC firm, which has an office in Toronto, had been chatting with Dan Durocher," Sfeir says. They decided it would be a good idea to combine both, so Pol θ would be the lead target, but at the same time, the CRISPR platform would be identifying additional targets that would be screened for chemical inhibitors and taken into the clinic.

And in March, 2016, only two years after Sfeir's *Nature* paper[16] describing Polθ appeared, Repare was launched, with Versant partnering with MPM Capital to lead a $68-million A round. That round included backing from Celgene, FTQ Ventures (Montreal) and BDC Ventures (Montreal). Repare CEO Lloyd Segal, previously a managing partner at Persistence Capital Partners (Montreal), helped create the startup while he was an entrepreneur-in-residence at Versant.

Barbara Weber, Tango CEO

Elsewhere, another startup, Tango Therapeutics, is also screening for synthetic lethals to identify new drug targets for subgroups of cancer. In Tango's case, the plan is to target specific mutations in tumor suppressor genes, oncogenes and immune evasion genes. "Once you understand which genes can help the tumor evade being killed by the immune system, you can do a modified screen for synthetic-lethal-like drug targets. Drugs against those targets should reduce immune evasion in those cancer subtypes— what is sometimes referred to as making cold tumors hot," says Barbara Weber, CEO of Tango and a venture partner at Third Rock Ventures (Boston). In other words, tumors resistant to checkpoint inhibitor treatment may finally be targetable.

Tango aims to leverage advances in DNA sequencing and CRISPR-based target discovery. Using tumor sequence information, they will identify subgroups of cancer patients according to which mutations are driving their tumors. They will then use CRISPR screens in either cancer cell lines or animal models to identify novel targets that are synthetic lethals with the defining genetic mutation in each subgroup.

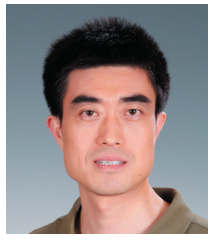
It all started, Weber explains, when Alan Ashworth—now at the University of California, San Francisco—demonstrated the concept of synthetic lethality in BRCA-mutated breast cancer using PARP inhibitors[17]. "Alan and I, as well as others, have been talking about this field for ten years," she says. "But the approach could not be taken to scale with siRNA [short interfering RNA] because of its off-target effects." CRISPR came along and opened up the door.

In March 2017, Tango received a $55-million series A investment round from Third Rock Ventures, which had been incubating the company for the preceding 18 months. Like most Third Rock companies, Tango is built "with the involvement of key academic investigators who had been working on synthetic lethality in cancer, and assembled them to build a company organically," says Weber, who, as venture partner at Third Rock since 2015, led the group that built the company. Co-founders include Timothy Lu of Massachusetts Institute of Technology in Cambridge, Massachusetts, a bioengineer with expertise in CRISPR–Cas9; Jose Baselga of Memorial Sloan Kettering Cancer Center in New York, who works on targeted cancer therapies and drug resistance; Levi Garraway of Eli Lilly of Indianapolis, who works on cancer genomics; Bill Kaelin of Dana-Farber Cancer Institute in Boston, whose research has focused on mutations in tumor-suppressor genes, Toni Ribas of the University of California Los Angeles, who uncovered mutations that confer resistance to the breakthrough immunotherapy PD-1; and, of course, Ashworth.

Weber says that the platform is up and running and the data thus far have been very encouraging. Tango has moved several novel targets forward into its drug discovery program. Their CRISPR-based screen of RAS-mutant lung cancer cells provided evidence for the known role of mitogen-activated protein kinase (MAPK) pathway signaling in this genetic context. However, among the top five hits in the CRISPR screen they discovered a novel target that has not been considered before, even in this very well-studied pathway. "We are seeing targets that are not discoverable without this approach," she says. "These are some of the more interesting targets I've seen in some time. The biology immediately makes sense. We are not discovering targets and then saying, 'I wonder why that works?'"

Weber says they intend to grow Tango into a fully integrated biopharma, although they are looking for one or two dedicated pharma partners who share their vision. "But we don't intend to do fee-for-service screening." Looking ahead, she says the biggest challenge is long timelines to do drug discovery. "It just takes a certain amount of time to get from a drug candidate to the clinic."

A sign of the global interest in synthetic lethal screening using CRISPR is the appearance of two new companies in Asia, one in Tokyo and the other in Beijing, to take advantage of the technology. Confusingly, they both bear the same name EdiGene. The first of the two to be founded, was a Chinese startup, raising $10 million in a series A round in late 2016. The company's founder and chief scientific advisor, Wensheng Wei, an investigator at Peking University, is among the early developers of CRISPR screens



Wensheng Wei, EdiGene founder

for studying functional genomics[18]. Wei has assembled a team with expertise in functional genomics.

One focus of Wei's laboratory has been on long non-coding RNAs (lncRNA), a large, relatively unexploited and uncharacterized segment of the transcriptome. His lab has created a library of paired guide RNAs for conducting high-throughput deletion screening, targeting over 700 lncRNAs. In published work, Wei's team found several lncRNAs with oncogenic or tumor suppressor activities[19]. Wei says the same system can be used to screen for synthetic lethals, and is working on optimizing his system. "With synthetic lethals, the bottleneck is too many combinations, so people are trying every possible way to increase coverage as efficiently as possible," he says.

Wei says the company is still at an early stage, and he and his staff are interested in providing whatever services they can to researchers and to companies. Ultimately, though, they intend to exploit their technologies as drug discovery platform using CRISPR lethal screening technologies of both protein-coding genes and lncRNAs with therapeutic potential. "We think the series of high-throughput technologies can change the model of drug discovery, help us understand drug resistance. It could be a huge advantage over conventional drug discovery," he says.

Stephen Friend, chairman of the board of Sage Bionetworks (Seattle) and co-founder and president of 4YouandMe (Seattle), who with Nobel laureate Leland Hartwell, recognized the power of synthetic lethal strategies in human disease nearly 30 years ago[20,21], is delighted that the approach is finally getting traction. "What a treat," he says. "It looks as if the concept, the power, the productivity, the usefulness of synthetic lethals are beginning to find the light of day." Friend says it's not just CRISPR that is making this possible, but decades of work on developing systems biology capability, which enables the cellular interconnectedness to be determined. "It's now no longer scattered gene lists, it's no longer someone's work in the lab around the WNT pathway or EGFR pathway. It's a way of not just finding context but understanding the biological significance of the context," he says.

But, cautions Rene Bernards, cancer researcher at The Netherlands Cancer Institute (Amsterdam), who was an early developer of RNAi screens for exploiting synthetic lethals, the competitive edge must come from using unique model systems that allow one to gain new insights in relevant biological pathways. "The whole field must now move beyond the obvious. Whether you address such questions with CRISPR, shRNAs or haploid cells is in my view irrelevant, it is the biology that matters, not the technology," he says. *MAB & LD*

Thijs Rooimans

Sebastian Nijman and Thijn Brummelkamp, Scenic Biotech co-founders

Scenic Biotech: mapping out interacting pathways

A new and powerful approach pinpoints disease-modifying genes. In 2012, Sebastian Nijman and Thijn Brummelkamp, friends and colleagues since graduate school, put their toes in the commercial waters, and formed a company, Haplogen, to screen the human genome for host proteins that enable viral infections. This contrarian approach of controlling infections by targeting the host, rather than viral proteins, has been the hallmark of this duo, as the two colleagues in their latest startup, Scenic Biotech, are going against a current craze. Whereas a cadre of newly minted biotechs are developing screens for finding synthetic lethal gene combinations, Scenic has created a screening platform for identifying interactions that will restore health in diseased cells.

As described in a 2017 *Nature* paper[22], the screen is conducted in the human haploid cell line HAP1, which Brummelkamp and colleagues developed when he was a Whitehead Fellow[23]. It employs a retroviral gene trap to generate large populations (greater than 10^8) of mutagenized cells, which they then interrogate for proteins associated with particular phenotypes or functions. Mutations in genes that increase or decrease the abundance of the protein of interest are compared and quantified. "Using this technology, we can now generate nearly comprehensive maps of genes that affect a protein in normal cells. This becomes even more insightful when we repeat the experiment in cells that lack a specific regulator, such as a gene mutated in disease. By comparing these maps we can find genetic suppressors that modify the phenotype only in diseased cells," explains Brummelkamp.

Nijman likes to call what they are doing mapping, rather than screening. "Screens imply that often you miss quite a lot, you create a lot of false positive[s] and negatives," he says. With their 'CellSeq' platform, they can sensitively assign genetic regulators to any protein that can be measured, offering more phenotypes that can be examined than assays focused on cell growth and viability. Because hundreds to thousands of mutants are created per individual gene, this generates very sensitive readouts. The resulting 'regulator maps' can be compared in different ways: between readouts or between genotypes. Nijman says that when he saw how robust the screen was, "That for us was the point of 'Wow! This is really something new'. Because nobody has been able to do that in human cells at the scale and precision that we could."

Scenic's approach can be applied to identifying mutants that control processes in normal cells, but it can also be applied in reverse, and find mutants that can normalize diseases that have readable phenotypes. Such genes, referred to as genetic suppressors, have been shown to modulate phenotypes in yeast and *Drosophila*. The hope is that such genes might be enlisted to alleviate severe human diseases. However, finding them in the human genome has been more challenging. Although work by Eric Schadt's group identified rare individuals harboring these loci[24], there hasn't been a way to tease out the precise molecular mechanism underpinning disease modulation or suppression. Nijman and Brummelkamp believe that Scenic's technology can start to unravel some of these genetic suppressor networks.

"We can say, look, here are all the genetic interactions. Many of them will not be attractive drug targets, but if we repeat this [a] number of times, for sure we will identify drug targets. We are excited about the concept of genetic suppressors as drug targets," says Nijman.

Once the two founders had worked out the concept, they took it to the European venture capitalist community, and with backing from BioGeneration Ventures, INKEF Capital and Oxford Sciences Innovation, SB was launched with a €6.5-million series A round of funding. This was a new experience for them, as with Haplogen, they had worked with an angel investor. "It took a lot more convincing this time," says Nijman. Haplogen's investors were convinced after one meeting.

Lysosomal storage diseases will be one area that Scenic will target because not only do many genes associated with these severe illnesses cause pronounced phenotypes, but also the molecular pathways are well recapitulated in their HAP1 cell line. "We are limited to one model, so there are certain areas of biology that we can't cover. But there are many that we can, such as lysosomal storage diseases," says Brummelkamp.

Scenic is interested in two types of partner-

ships: first, with researchers that share an interest in a particular disease, such as lysosomal storage diseases, that dovetails with their platform; and second, with researchers interested in specific targets.

Friend, who recently joined Scenic's scientific advisory board, says that Scenic's power comes from "building up a database that has enough snapshots of what happens when you perturb different parts of the cell. A singular experiment is not being interrogated but it's the nest or the compendium of queries that are being observed." However, he cautions, "A turn of the crank is cheap. What's behind it is making sense of that which comes out of it. It assumes we know all those connections and we still don't know all those connections," he says. Understanding those connections is at the heart of Scenic Biotech's mission. *LD*

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