often require multiple or large doses for effective inhibition. And finally, even degronimids with low binding affinities could be effective as, once the target protein is degraded, the binder is released and can bind again, acting catalytically. "This is one of the magical things about this drug, you can use sub-stoichiometric amounts of the drug—really a tiny amount can bind to its target, kill it and then come off and bind to another target and kill that," says Jaffrey.

Potentially, anything that binds proteins could be hooked up to an imide. Phillips says, "If there's a binder out there we can turn it into a degrader and very quickly start to understand the pharmacology. It gives us an opportunity to shorten the discovery path that leads to drugs." To find binders, Phillips says that they are searching the literature of known chemical space, as well screening for binders and designing some from scratch.

C4 was put together by Marc Cohen, the executive chairman, who, as a trustee at Dana Farber, has worked along with the institute's technology transfer group to find support for promising lines of work. "I'm particularly interested in accelerating the translation of discoveries, from the bench to the clinic, not leaving things hanging around on the shelf," says Cohen. In January 2016, the company launched with $73 million in a series A round from Cobro Ventures (Fairfax, VA, USA), a discovery venture firm founded by Cohen, and some super-angels. At its founding, C4 announced a partnership with Roche for undisclosed oncology targets potentially worth $750 million (upfront money was not disclosed).

Much remains to be worked out, according to Jaffrey. Right now, the strategy has been shown to work with only a few E3 ligases, those to which the imide binds. One question is whether degronimids can be developed that use other ligases, potentially some that are tissue specific. Also, the phthalimides could have some toxicities (class effects) that would show up when applied systemically. Expanding the chemistry to other ligases might help here, if they provide tissue specificity. Finally, the rate at which target proteins are degraded will have to exceed the target's rate of synthesis, particularly in the case of weak binders. These parameters will have to be established for each target, says Jaffrey.

Phillips, a native New Zealander who came to the United States 20 years ago as a postdoc, finds Cambridge a fabulous place to do science. And when he heard about Bradner's work, his first thought was: "Will it be a company?" The second: "How do I get a ticket on this train?" He says, "It's something that, to me, was honestly the best opportunity I've ever seen."

Now 50 people strong, the company is deeply invested in oncology with its Roche partnership, but it is also looking to targets in infectious diseases and other indications. At the moment, Phillips feels that there's tremendous excitement in the space, but so far, they have only a handful of tools in the toolkit. "To really make the difference on the scale we'd like to impact, we need additional tools. We need to know which E3 ligase is the next cereblon," he says. ***LD***

Gadeta: extending the reach of CAR T cells

By targeting the γδ T cell receptor, Gadeta combines immunotherapy with metabolomics. Chimeric antigen receptor T cell (CAR-T) therapies are electrifying the cancer field but have so far been aimed only at CD19-bearing malignancies. Progress in other cancer types, particularly in solid tumors, has been stymied by a lack of suitable targets as well as insufficient homing of CAR-T cells to tumor sites and poor persistence of the transplanted cells[17]. Dutch biotech firm Gadeta (Utrecht), a spinout from the University Medical Center Utrecht (UMC Utrecht), is putting a new twist on adoptive T cell therapy, by grafting T cell receptors (TCRs) derived from γδ T cells (γδ TCRs) onto conventional T cells, which ordinarily express α and β TCR chains. This approach, originally developed in the lab of Jürgen Kuball, Gadeta's scientific founder and CSO, could bring a new set of tumor-associated antigens into play, at the same time building on the manufacturing and clinical development know-how the CAR-T cell therapy field has generated. This theory will soon be put to the test in a clinical trial of αβ T cells engineered to express a γδ TCR in leukemia or multiple myeloma set to get under way this year.

Jürgen Kuball, Gadeta CEO

First discovered in the 1980s, γδ T cells combine characteristics of both the innate and adaptive immune systems. Unlike αβ TCRs, γδ TCRs do not require major histocompatibility complex (MHC) molecules to recognize their target antigen. Along with innate immune effector cells, γδT-cells respond rapidly to cellular stress or infection, before an αβ T cell response emerges. Although they constitute a minority of circulating T cells in the blood, γδT-cells are highly abundant in epithelial tissues[18]. They appear to have a key role in cancer immune surveillance by recognizing newly transformed cells during the initial steps of tumorigenesis. "Each time a cell turns out funny, these cells kick in," says Kuball, who also chairs the adult hematology department at UMC Utrecht. An unexpected finding from a recent gene expression analysis of 18,000 human tumors has further galvanized interest in their therapeutic potential. The study, led by Ash Alizadeh at Stanford University, found that the presence of γδ T cells in patients' tumors—inferred by computational analysis of bulk tumor transcriptomes—was associated with a better clinical outcome than the presence of 21 other leukocyte populations, across 25 different cancer types[19].

Early efforts to develop cancer therapies that employ γδ T cells foundered owing to poor persistence of the transferred cells[20]. "It's very hard to get them to proliferate," says Kuball. This is particularly difficult in patients with advanced cancer, even though they can readily mount αβ T cell responses to an infectious agent. His group's effort to use αβ T cells as carriers for γδ TCRs showed preliminary *in vivo* and *in vitro* proof of concept several years ahead of Alizadeh's findings[21]. "It was the first circumstantial evidence that we were able to target leukemic stem cells," he says. Since then, the company has developed a screening platform, combinatorial T cell receptor exchange (CTE), to identify optimized, high-affinity combinations of γ and δ TCR chains that respond to metabolic changes in cancer cells. "We're able to target not only hematological malignancies. The pathway we're targeting is a metabolic pathway that is active in many cancer cells," Kuball says. So far, the company has identified more than five candidate gδ TCRs that are at various stages of development.

The overall approach is not obvious, particularly as it is not clear precisely how gδ TCRs interact with their targets. "Intuitively, it doesn't make a lot of sense. If it works, it's cool," says Immo Prinz at the Institute of Immunology, Hanover Medical School (Hanover, Germany). "It's possible that the threshold to activate these chimeric αβ T cells is lower," he says. "That could be the big advantage." Long-term persistence of the transplanted cells appears not to be a problem in challenge experiments, Kuball says, although clinical trials will have to determine whether this holds true in humans.

Kuball was joined as co-founder and CEO by Marc DeBoer, venture partner at London-based Medicxi Ventures (previously the life sciences arm of Index Ventures), who had to overcome his initial skepticism. "My first

perception was those cells were difficult. What do they recognize?" he recalls. He became increasingly intrigued—particularly, he says, as he learned more about how γδ TCRs interact with their targets. "γδ T cell receptors seem to recognize their targets more like an antibody in a protein–protein interaction," he says. As a self-described "antibody guy," he found this an attractive proposition. However, the financing strategy for building out Gadeta's cell therapy approach is radically different from what an antibody development program requires. Medicxi—and Index before it—is closely associated with an asset-centric financing model, which typically involves the creation of a virtual company around a single program. DeBoer is conscious of the need to build out the company's technology platform, which requires an in-house scientific team, as well as Kuball's research group at UMC Utrecht.

The company is currently expanding its staff and has enough cash, including an innovation loan from the Dutch government, to take it through a first clinical readout. Its strategic plan, which covers the next three years, calls for a significant uptick in investment. "We need about $40 million–50 million to really get solid proof of concept on the technology in solid tumors," DeBoer says. "We are comfortable we will raise the money in one or two steps, starting this year."

First out of the gate is an investigator-initiated study to treat patients who have leukemia or refractory multiple myeloma with TEG-001, an αβ T cell engineered to express a γδ TCR that is activated by butyrophilin-3A1, a conformation of CD277 that results from cancer-induced changes in cholesterol metabolism[22]. A company-sponsored trial of TEG-002, which also targets CD277, in solid tumors will follow in late 2018 or early 2019. ***CS***

Lodo Therapeutics: natural products from soil metagenomics

Heterologous expression of biosynthetic gene clusters identified via soil metagenomics opens the path to new chemical space. Microbes have been the starting point for drug discovery efforts for decades, at least since Alexander Fleming isolated penicillin from *Penicillium rubens* in 1929. More than 60% of all FDA-approved anti-infective and anticancer drugs have been derived from environmental microbes. But all have come from microbes that can be cultured, leaving a huge untapped potential from the roughly 99% of soil microbes that cannot be cultured. Lodo Therapeutics (New York) is applying its large-scale metagenomic profiling technologies to uncover bioactive compounds from soil microbes that so far have been overlooked.

Lodo was founded on the basis of work done by Sean Brady, head of The Rockefeller University's Laboratory of Genetically Encoded Small Molecules. Brady has spent eight years devising the most efficient way to access natural molecules from unculturable soil bacteria. He starts with DNA isolated directly from soil, which can contain upwards of 10,000 different microbial species. Then, using a mix of degenerate primers of similar, but not identical, sequences, Brady conducts PCR on the soil DNA samples to find motifs that are conserved across biosynthetic pathways of interest. These motifs are sequenced to generate what he calls natural product sequence tags (NPSTs) and compared to other bacterial genomic sequences using computational searches of curated genetic reference databases. Based on these *in silico* searches, Brady can prioritize which soil samples have the highest chances of containing novel biosynthetic gene clusters of interest, including those from cryptic DNA. He then creates large-insert (40 kb) cosmid libraries for discovery studies. The cloned gene clusters can be engineered into model microbes and heterologously expressed, and the resulting biosynthetic compounds isolated and characterized. "We've essentially figured out a way to clone and sequence whole environments, and then pull out biosynthetic gene clusters of interest to discover new compounds," Brady says.

Sean Brady, Lodo founder

Using this platform, his team has identified several novel compounds as potential starting points for new therapeutics. For example, they searched for epoxyketone proteasome inhibitors from 185 soil samples from around the world and found 99 unique epoxyketone NPSTs. They were then able to recover nine complete gene clusters associated with the NPSTs. Heterologous expression in five *Streptomyces* host strains yielded seven potent epoxyketone proteasome inhibitors, including some with novel warhead structures and a naturally occurring halohydrin prodrug[1].

Although these various technologies are not proprietary, Brady has been able to scale them up to analyze hundreds of soil samples in a month. "About three years ago, I decided that what we'd developed in the lab had to move out of the lab in order to scale it up and translate into real drug discovery," Brady says. Around that time, he serendipitously caught the eye of the Bill and Melinda Gates Foundation (Seattle), which provided funding for his lab to discover compounds for treating tuberculosis—a global health problem due in part to the emergence of multidrug-resistant strains. Rockefeller University's technology transfer office reached out to Accelerator Corporation (Seattle), which is a syndicate of venture capital investors including ARCH Venture Partners (Chicago) and state funds such as the Innovate NY Fund and others. In January 2016, Accelerator launched Lodo with a $17-million series A round.

Lodo is maintaining its initial focus on tuberculosis. The company's lead compound is undergoing optimization, which has increased its activity against drug-resistant strains. Lodo is also looking for compounds against Gram-negative bacteria, an area with great unmet medical need. CSO and co-founder David Pompliano, a partner at Apple Tree Partners (New York), points out that there are evolutionary reasons to focus on leads derived from antibacterial natural products. "Molecules developed by nature are under selection pressure. One pressure is an arms race for microbes to develop antibiotics to kill other microbes, then those microbes develop resistance to those antibiotics, and new antibiotics evolve, and then more resistance and on and on. We have found some compounds that look like they will overcome resistance," Pompliano says.

The New York–based startup plans to expand its efforts into indications such as oncology and immune-related diseases, for which many treatments have been derived from soil microbes. Pompliano notes that the interplay between humans and microbes has existed since humans first evolved, and bacteria have evolved ways to suppress inflammation and the immune response. UCSD's Rob Knight agrees that Lodo's initial disease areas "are good places to start." He added that he is aware of other companies attempting to mine the soil metagenome using an approach similar to that of Lodo, "including major agribusinesses."

One company with a head start on Lodo is Warp Drive Therapeutics (Cambridge, MA, USA), which launched, to great fanfare, in 2012. To date, Warp Drive has focused its efforts on discovering novel natural products against drug-resistant infectious agents. It has amassed a database of 135,000 actinomycete genomic sequences, containing 148 complete genome sequences and 148 biosynthetic gene clusters that encode the enzymes to make ~3.5 million natural products. Last November, the company achieved its first milestone, providing a set of novel aminoglycoside antibiotics to Sanofi (Paris).

1. Oldenborg, P.-A. *et al.* Role of CD47 as a marker of self on red blood cells. *Science* **288**, 2051–2054 (2000).
2. Jaiswal, S. *et al.* CD47 is upregulated on circulating hematopoietic stem cells and leukemia cells to avoid phagocytosis. *Cell* **138**, 271–285 (2009).
3. Majeti, R. *et al.* CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. *Cell* **138**, 286–299 (2009).
4. Chao, M.P. *et al.* Calreticulin is the dominant pro-phagocytic signal on multiple human cancers and is counterbalanced by CD47. *Sci. Transl. Med.* **2**, 63ra94 (2010).
5. Horrigan, S.K. Replication study: the CD47-signal regulatory protein alpha (SIRPa) interaction is a therapeutic target for human solid tumors. *eLife* **6**, e18173 (2017).
6. Willingham, S.B. *et al.* The CD47-signal regulatory protein alpha (SIRPa) interaction is a therapeutic target for human solid tumors. *Proc. Natl. Acad. Sci. USA* **109**, 6662–6667 (2012).
7. Kojima, Y. *et al.* CD47-blocking antibodies restore phagocytosis and prevent atherosclerosis. *Nature* **536**, 86–90 (2016).
8. Palchaudhuri, R. *et al.* Non-genotoxic conditioning for hematopoietic stem cell transplantation using a hematopoietic-cell-specific internalizing immunotoxin. *Nat. Biotechnol.* **34**, 738–745 (2016).
9. Hsiao, E.Y. *et al.* Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell* **155**, 1451–1463 (2013).
10. Sampson, T.R. *et al.* Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. *Cell* **167**, 1469–1480.e12 (2016).
11. Lee, J.H. *et al.* Highly multiplexed subcellular RNA sequencing in situ. *Science* **343**, 1360–1363 (2014).
12. Munger, J.S. *et al.* The integrin alpha v beta 6 binds and activates latent TGF beta 1: a mechanism for regulating pulmonary inflammation and fibrosis. *Cell* **96**, 319–328 (1999).
13. Horan, G.S. *et al.* Partial inhibition of integrin alpha(v) beta6 prevents pulmonary fibrosis without exacerbating inflammation. *Am. J. Respir. Crit. Care Med.* **177**, 56–65 (2008).
14. Krönke, J. *et al.* Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. *Science* **343**, 301–305 (2014).
15. Krönke, J. *et al.* Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. *Science* **343**, 301–305 (2014).
16. Winter, G.E. *et al.* DRUG DEVELOPMENT. Phthalimide conjugation as a strategy for in vivo target protein degradation. *Science* **348**, 1376–1381 (2015).
17. Dai, H., Wang, Y., Lu, X. & Han, W. Chimeric antigen receptors modified T-cells for cancer therapy. *J. Natl. Cancer Inst.* **108**, djv439 (2016).
18. Bonneville, M., O'Brien, R.L. & Born, W.K. Gammadelta T cell effector functions: a blend of innate programming and acquired plasticity. *Nat. Rev. Immunol.* **10**, 467–478 (2010).
19. Gentles, A.J. *et al.* The prognostic landscape of genes and infiltrating immune cells across human cancers. *Nat. Med.* **21**, 938–945 (2015).
20. Fournié, J.J. *et al.* What lessons can be learned from gδ T cell-based cancer immunotherapy trials? *Cell. Mol. Immunol.* **10**, 35–41 (2013).
21. Marcu-Malina, V. *et al.* Redirecting aβ T cells against cancer cells by transfer of a broadly tumor-reactive gdT-cell receptor. *Blood* **118**, 50–59 (2011).
22. Sebestyen, Z. *et al.* RhoB mediates phosphoantigen recognition by Vγ9Vδ2T cell receptor. *Cell Rep.* **15**, 1973–1985 (2016).
23. Choi, C.H., Hao, L., Narayan, S.P., Auyeung, E. & Mirkin, C.A. Mechanism for the endocytosis of spherical nucleic acid nanoparticle conjugates. *Proc. Natl. Acad. Sci. USA* **110**, 7625–7630 (2013).
24. Radovic-Moreno, A.F. *et al.* Immunomodulatory spherical nucleic acids. *Proc. Natl. Acad. Sci. USA* **112**, 3892–3897 (2015).
25. Wang, J. & Quake, S.R. RNA-guided endonuclease provides a therapeutic strategy to cure latent herpesviridae infection. *Proc. Natl. Acad. Sci. USA* **111**, 13157–13162 (2014).