Synthetic biologist Christina Smolke co-founded Antheia to develop alternative ways to make opioid drugs.

ROD SEARCEY/STANFORD ENGINEERING

THERAPEUTIC DEVELOPMENTS

Masters of medicine

Drawing on the latest research, companies are developing more-effective therapies.

ANTHEIA
Lab-made opioids

Stanford University, California

News about opioids usually revolves around crime, addiction and death. Overdoses of drugs such as heroin and oxycodone killed more than 28,000 people in the United States in 2014. And in Europe, 70% of people who seek treatment for addiction are dependent on opioids.

What these headlines obscure is the value of the drugs in relieving pain caused by childbirth and surgery or conditions such as cancer and heart disease, says synthetic biologist Christina Smolke at Stanford University in California. Many people are suffering because they lack access to opioids. According to the International Narcotics Control Board, 5.5 billion people have limited or no access to essential painkillers, including the opiates codeine and morphine. "There is a need for a technology to reduce the cost and reduce the barriers to access," says Smolke.

Smolke is also chief executive of Antheia, the start-up she co-founded to develop a less-expensive, and perhaps less-addictive, supply of these drugs. Instead of producing opiates from poppies, Antheia fills fermenters with bioengineered yeast and feeds the microorganisms sugar. The fermenters aren't subject to the vagaries of weather, pests, climate change and other risks that poppy crops are. "This is a platform that is intrinsically scalable and accessible to people around the globe," says Smolke. "We are building out a new capacity to make medicines."

Antheia is entering a complex field. Not only must it deal with the usual challenges associated with scaling up synthetic processes and competing with established technologies (something many other synthetic biology start-ups have failed to do) and comply with the strict laws that surround narcotics, but the company must also pull off some especially difficult bioengineering.

COMPLEX PATHWAY

Opium from poppies is the source of morphine, codeine and thebaine. Morphine and codeine are useful in themselves for treating pain and suppressing coughs, for example. And pharmaceutical chemists can use all these opiates (and other non-narcotic alkaloids derived from poppies) to make other pain-relieving drugs, including fentanyl and oxycodone. But chemists can't readily make the core opiate structures in the lab.

Benzylisoquinoline alkaloids — the group of compounds that includes opioids — have "lots of chirality", says Smolke. Chiral molecules can exist in two or more forms, called isomers, the structures of which are mirror images of one another. Only one isomer will fit into opioid receptors in cells. Synthetic catalysts are not specific and typically produce a mix of isomers that must be painstakingly purified to yield a particular form. Biological systems, however, such as the plant enzymes involved in opiate production, are adept at telling chiral isomers apart, making opioids good candidates for biosynthesis.

Smolke's lab was the first to engineer yeast to produce these alkaloids. The opioid pathway is one of the most complex built by synthetic biologists, involving around 20 genes from poppies, mammals, bacteria and the fermenting yeast themselves. In its

proof-of-principle work (S. Galanie *et al. Science* **349,** 1095–1100; 2015), Smolke's group made thebaine and hydrocodone.

When Smolke began trying to synthesize opioids in yeast some ten years ago, experts told her "this is impossible", she recalls. She pressed on with the research anyway, developing the tools to make it possible. Her group found the gene for the remaining key enzyme in a genetic database in 2015.

The paper describing the complete opioid-production pathway reads like an anti-business case for Antheia. It points out that a single dose of hydrocodone would require thousands of litres of fermentation broth. And Smolke says that she and the editors at *Science* wanted to make sure they weren't publishing something dangerous — a recipe for potential morphine home brewers.

The researchers had estimated that they would need to improve the process's overall yield by around 7-million-fold to feasibly convert sugar to morphine. Smolke went on leave from Stanford in 2015 to build the company and lead work on improving yields. "I believe very strongly in our mission," she says. Stanford's administration is well-known for its support of faculty and students who start companies (Hewlett-Packard, Cisco Systems, Yahoo and Google all originated at Stanford).

Antheia has a small lab space in Menlo Park in California's Silicon Valley. There, scientists fine-tune what synthetic biologists call a yeast chassis. The analogy comes from the car industry: a cell can be a chassis, a framework that different parts, or genes, can be added to or taken away from to engineer something useful. But often it's not as simple as screwing a new part onto a car frame; the Antheia team must retool its chassis to deal with compatibility issues between yeast, plants and other organisms.

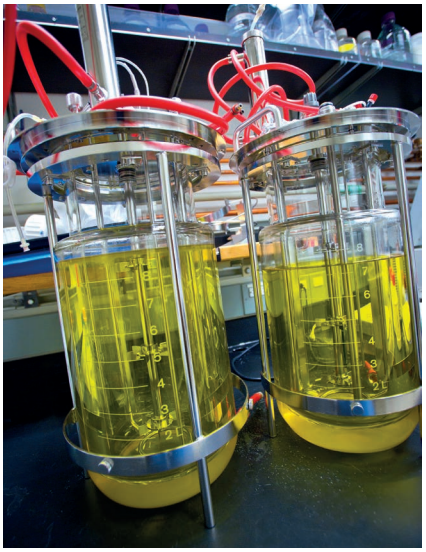
Plant cells have different regulatory mechanisms and organelles that don't exist in yeast. "Plants do all these things you don't find in microorganisms, so we have to recode these enzymes to be functional in yeast," Smolke says.

Even with all the right enzymes in place, unforeseen hurdles pop up in most biosynthesis projects. This is something Jay Keasling, a synthetic biologist at the University of California, Berkeley, who is not involved with Antheia, has experienced. When his company Amyris was developing a synthetic version of the antimalaria drug artemisinin, it had to work out how to prevent one of the necessary enzymes killing the yeast cells with reactive oxygen. "If you don't get the balance right," he says, "the enzymes themselves can be toxic."

REMAKING THE DRUG INDUSTRY

If it seems that Antheia is starting with the most difficult problem possible, it is to some extent by design. "As we work with this extremely complex case, we're building out our know-how," Smolke says. "We can then take that knowledge and apply it to other pathways."

She has broader ambitions than just opioids. "Opioids are the classic case of how nature can be an unstable source of a compound that's medically critical and chemically difficult," she says. Many crucial medicines such as antibiotics and cancer drugs also fit this profile.



ROY KALTSCHMIDT/LAWRENCE BERKELEY NATL LAB.

Fermenters are filled with yeast and sugar.

Synthetic biology can streamline the production of many drugs, and once the process is refined it can be replicated wherever the drugs are needed. "You can go from one drug to the next without a big shift," says Keasling. This approach can also stabilize supplies of crucial medicines by decoupling them from agriculture.

Antheia plans to create new variations of opioids that could rid them of their addictive properties, as well as their side effects, such as constipation and slowed breathing. "We have the scaffold for bioactivity, now can we push for better profiles?" Smolke asks.

That's the right question, says Keasling. "That's been the vision of the field for a long time, but it's a long vision."

Keasling's artemisinic-acid pathway was published in 2006; the semisynthetic drug went on the market in 2013.

"It's very challenging to tackle all of this at once, especially as a start-up," says Smolke. Antheia is taking it one step at a time, with the short-term goal of bringing a biosynthetic alternative of an existing opioid to market. Smolke thinks that the company can realize this in less than five years. ■

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OXSTEM
Doubling down on disruption

University of Oxford, UK

When biologists first proposed stem-cell therapy, they thought that the injected cells would restore tissue damaged by disease by remaining in the tissue and steadily pumping out healthy daughter cells. But clinical trials have shown that the treatments don't always work as expected. In most cases, the injected cells are quickly flushed from the body, and even when they stay, they usually work by stimulating a regenerative response in other cells.

In those cases, "why do we need cell transplants at all?" asks Angela Russell, a medical chemist at the University of Oxford, UK.

That's the disruptive thinking behind OxStem, which was founded with the goal of treating age-related diseases by regulating stem cells with small-molecule compounds. OxStem launched last year with first-round funding of £16.9 million (US$21.1 million) — which the company says is a record for a UK academic start-up. The company has an unusual corporate structure: research is carried out at the university and is funded by OxStem or its subsidiary firms, which have the rights to bring the fruits of this research to market.

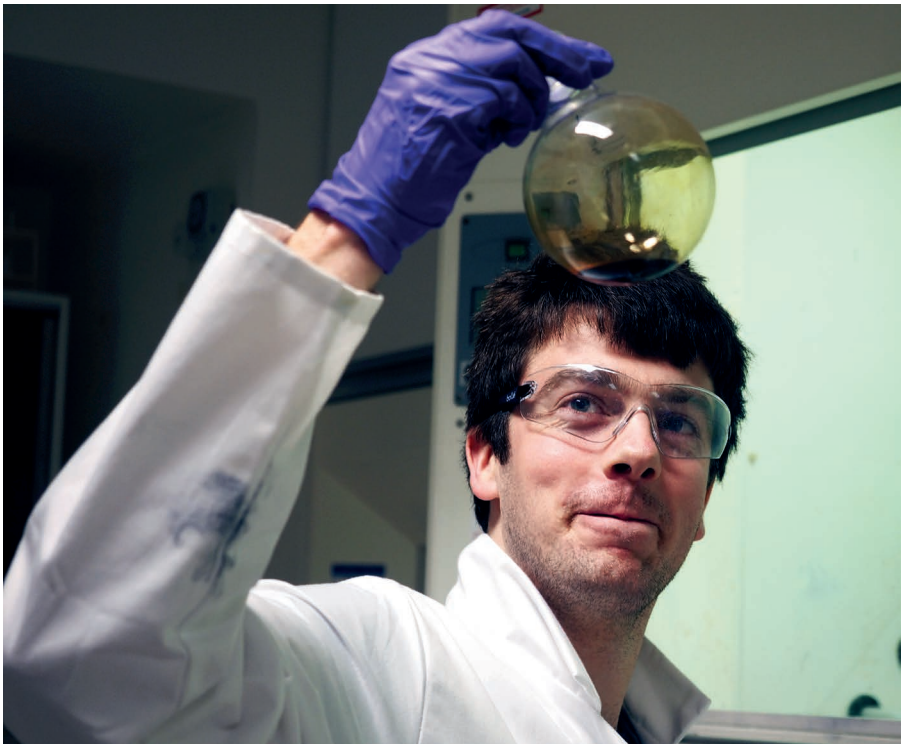
CLEANING THE SCREENS

For more than 20 years, biomedical researchers have studied a range of stem cells — from embryonic stem cells and induced pluripotent stem cells (those derived from adult cells with near-embryonic states) to adult stem cells that go haywire in blood cancers, as well as adult progenitor cells. But drug developers have struggled to apply standard compound-screening techniques to these cells.

Russell works with Stephen Davies, an organic biochemist at Oxford, to identify molecules that can alter the fate of stem cells. "Years ago, we developed a technology that allows you to stabilize undifferentiated cells and grow them up in culture," Russell says. "It's a technology to allow us to actually screen the compounds that induce the differentiation that we want to see in people."

In 2003, Davies co-founded a company with Oxford genomics researcher Kay Davies. This evolved into drug-development firm Summit Therapeutics in Abingdon, UK. Summit is now running phase II clinical tests of a small-molecule drug aimed at boosting protein production to treat Duchenne muscular dystrophy, a rare genetic disease.

Together with Russell, in 2014 the researchers proposed a spin-off company



MATTHEW VAUGHAN/OXSTEM

Chemist Liam Bromhead is doing an OxStem-funded postdoc at the University of Oxford.

with a broader scope — OxStem — to Oxford University Innovation (OUI), the university's technology transfer company.

Oxford typically retains a stake in its spin-offs. "The university sees itself as an equal founder together with the academics and the investors," says Carolyn Porter, deputy head of technology transfer at the OUI and an OxStem board member. "Our emphasis is on societal impact, not necessarily financial gain."

With OxStem, Stephen Davies proposed that the university also retain the pre-clinical research. This would bring substantial funding back to the university and make it easier for OxStem to recruit scientific talent, says OxStem's chief executive Michael Stein, a physician-turned-entrepreneur. The arrangement would also allow the fledgling company to take advantage of the chemistry department's extensive lab facilities. "You couldn't do this commercially without spending ridiculous amounts of money on the infrastructure," says Stein.

> ***"The university sees itself as an equal founder together with the academics and the investors."***

"We've been able to persuade the university that we cannot succeed commercially without having an impact on society, and that makes it a perfectly harmonious relationship," he adds. "That's now a metric in the UK university system — what are you actually giving back to society, how are you translating these discoveries into something meaningful for the benefit of the world?"

OxStem's four subsidiaries target major disease areas: cancer, neurological conditions, cardiovascular disorders and eye disease. This corporate organization is "very attractive to investors," says Porter. "They are investing in a parent company that then is looking at parallel streams of research, with multiple shots on goal."

OxStem's co-founders all have experience of starting companies. Their extensive networks helped to enlist prominent backers such as genomics entrepreneur Craig Venter, who is on the scientific advisory board. "We could have raised double the amount of money that we did," says Stein. "Our investors are not out for the short term, which is a very different model from venture capitalists or traditional funds."

PROVING THE PRINCIPLE

Last December, the OxStem Neuro subsidiary provided a proof of principle for the drug-development strategy. Co-founder Francis Szele, a developmental biologist at Oxford, led the effort, which began by isolating neural stem cells from the hippocampus region of the brain. "We can grow these things up, apply phenotypic screening, isolate a compound, put that compound into an animal and get the effect we're looking for," Stein says. "That was pretty amazing."

This early finding goes some way to allaying a major concern: whether such treatments can selectively activate just one type of resident stem cell. "There are two nests of stem cells in the brain, and we've already showed that the compounds we've developed just target one," Russell says. As in all stem-cell therapies, the other worry is accidental tumours. "We need to be extremely careful to make sure we're not just pulling out compounds that cure the patients but give them cancer," she explains.

OxStem is not the only firm working on small-molecule drugs that target stem cells. Neuralstem in Germantown, Maryland, for example, has a drug in a phase II clinical trial that is intended to treat depression by creating neurons. But OxStem's goals may be the more ambitious. According to Stein, by the middle of the year, the company will have 39 principal investigators and postdoctoral researchers, with roughly twice as many collaborators in four university departments. And Stephen Davies is looking forward to creating more subsidiaries to attack other diseases. "This really is a conveyor belt," he says. ■

Eric Bender *is a freelance writer in Newton, Massachusetts.*

SYNLOGIC

Altered microbes to treat disease

Massachusetts Institute of Technology, Cambridge

James Collins and Timothy Lu didn't know what to expect when they arrived at Atlas Venture in Cambridge, Massachusetts, in 2013 to discuss their latest research on designing gene circuits in microbial cells. But almost as soon as the two synthetic biologists were finished speaking, a handshake deal to work with the venture-capital firm was in place.

"At the end of the meeting, they basically said, 'Guys, we want to do something with you in this space,'" recalls Collins, who was at Boston University in Massachusetts at the time and has since moved to the Massachusetts Institute of Technology (MIT), where Lu runs a lab.

For months, Collins, Lu and the team at Atlas brainstormed various applications for the researchers' technology, which involves rewiring bacteria to dynamically sense and regulate different molecular pathways. Much of the academics' work focused on building research tools or diagnostics, but the investors rejected those ideas. They wanted to build a new generation of living therapeutic that could treat everything from rare inherited metabolic disorders to inflammatory bowel disease and cancer.

Within a year of that first meeting, Synlogic was born, with intellectual property licensed from Boston University and

MIT, and almost US$30 million in initial funding from Atlas and venture-capital firm New Enterprise Associates in Chevy Chase, Maryland. A few months later, the Bill and Melinda Gates Foundation — which has provided Collins with funding to engineer bacteria that could detect and kill the pathogen responsible for cholera — supplied another $5 million.

"We were excited to find one of our investigators had moved forward in creating a company," says Charlotte Hubbert, a partner at Gates Foundation Venture Capital, the investment arm of the non-profit organization. Collins and Lu's technology, she adds, "has the capability to address issues in both the developed and developing world".

Synlogic has since raised a further $40 million, filed more than 160 patent applications and hired some 45 employees. Among the recruits is chief executive Juan Carlos Gutiérrez-Ramos, who was lured away from the pharmaceutical giant Pfizer, where he led biotherapeutics research and development.

Gutiérrez-Ramos is also a huge *Star Wars* fan, which explains why the conference rooms at Synlogic's headquarters are named after the fictional planets Coruscant, Alderaan, Endor and Hoth. Overlooking a row of red, black and white replicas of Stormtrooper helmets, Gutiérrez-Ramos explains his vision for the company. "Wherever someone has microbes that are non-pathogenic, we plan to act by empowering that microbial environment to do something that patients cannot do with their own bodies," he says.

A CAPITAL IDEA

Synlogic is not Collins's and Lu's first joint venture. Their first start-up, a company now known as Sample6, stemmed from research Lu and another co-founder, Michael Koeris, did as PhD students in Collins's lab — customizing viruses that infect bacteria to enhance their killing power. To drum up commercial interest, Lu and Koeris secured small grants through various university-sponsored competitions, ultimately winning around $100,000 in prize money. They leveraged this to raise close to $6 million from venture-capital firms. But this took a couple of years, and even then the company's initial round of funding was less than one-fifth of what Synlogic managed in 12 months.

Part of that speed is due to Atlas's access to capital. But according to Collins, the expertise of business-minded entrepreneurs at the firm was equally important.

Collins recalls the day that Dean Falb, an entrepreneur-in-residence at Atlas and co-founder of Synlogic, came to his office to suggest that the company deploy its synthetic microbes to remedy a class of genetic diseases known as inborn errors of metabolism. These rare inherited disorders are caused by defects in single genes that encode enzymes involved in breaking down various substances. Problems arise because of a build-up of toxic by-products.

Falb thought that Synlogic's microbes could help. Countless drugs and supplements already enter the bloodstream, but "pulling something that's bad out of the blood is much harder with a pill", says Falb. That's where Falb saw the technology having maximum impact. "It was really a brilliant insight by Dean and his team," Collins says.

SYNTHETIC PROBIOTICS

Three years on, Synlogic is now advancing products for two conditions: urea-cycle disorder and phenylketonuria. Both are marked by a person's inability to completely metabolize protein from his or her diet. Some medications can slow the effects of the diseases, and the disorders can be managed by low-protein diets, but patients often struggle to meet their metabolic needs.

The Synlogic therapies for urea-cycle disorder and phenylketonuria start with a strain of *Escherichia coli* called Nissle 1917. A German doctor isolated this bacterium from the faeces of a First World War soldier who was resistant to dysentery. It's now sold as a probiotic under the brand name Mutaflor to treat gastrointestinal problems such as constipation.

For urea-cycle disorder — a condition in which nitrogen accumulates in the form of ammonia — Synlogic used Collins's and Lu's research on toggle switches, logic circuits and other kinds of synthetic gene networks to modify the microbe's natural production of the amino acid arginine to go into overdrive in the oxygen-free environment found in the gut. Because making arginine requires the addition of nitrogen atoms, of which ammonia is a primary source, this genetic tweak should quickly eliminate the highly toxic substance from the body. Human trials are planned for later this year.

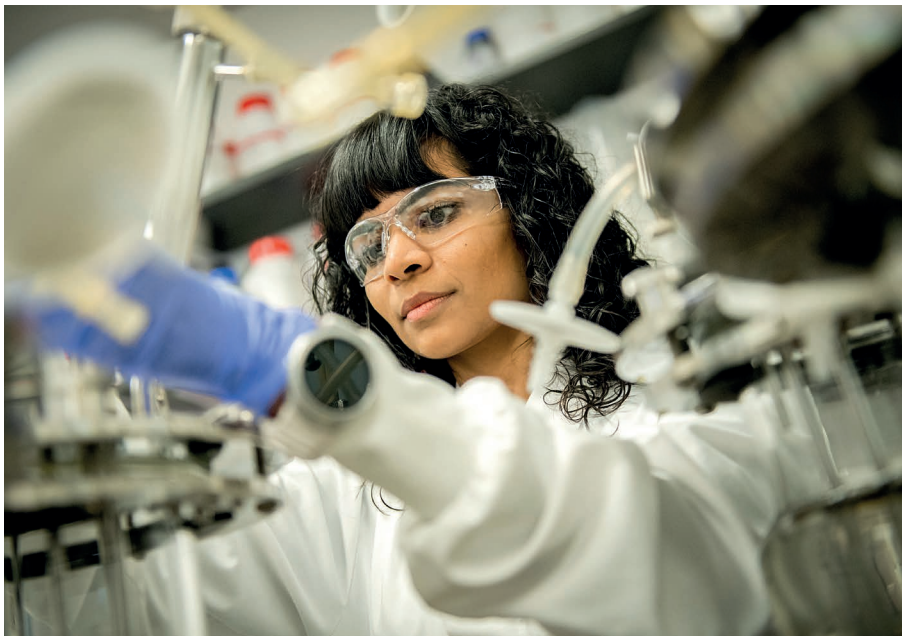
"Pulling something that's bad out of the blood is much harder with a pill."

For phenylketonuria, the company inserted an enzyme — also switched on under anaerobic conditions — that helps to break down the amino acid phenylalanine, which patients cannot otherwise metabolize. In both cases, "your microbiome is doing what the liver should be doing," says Gutiérrez-Ramos.

The company initially tested these engineered microbes in an anaerobic chamber nicknamed Emperor Palpatine, after another *Star Wars* character. It has since shown that the bacteria can blunt the increase of ammonia and phenylalanine levels in mouse models. Synlogic scientists presented the preclinical data in March at the annual meeting of the American College of Medical Genetics and Genomics in Phoenix, Arizona.

Synlogic has a deal in place with pharmaceutical company AbbVie in North Chicago, Illinois, to develop synthetic microbial medicines for Crohn's disease and ulcerative colitis. The plan is to engineer bacteria to respond to chemical signs of inflammation in the gut and produce remediating molecules. Bacteria that activate the immune system in the presence of cancer cells are also on the cards.

"It's really a platform technology," says Lu. "It can be applied now to rare diseases, but we're hoping to actually tackle some more complex diseases with the approach as well." ■



LIZ LINDER PHOTOGRAPHY/ WWW.LIZLINDER.COM

Process engineer Munira Momin scales up a synthetic strain in Synlogic's fermentation lab.

Elie Dolgin *is a freelance science writer in Somerville, Massachusetts.*

SAPIENCE THERAPEUTICS

Ticking the biological boxes

Columbia University, New York City

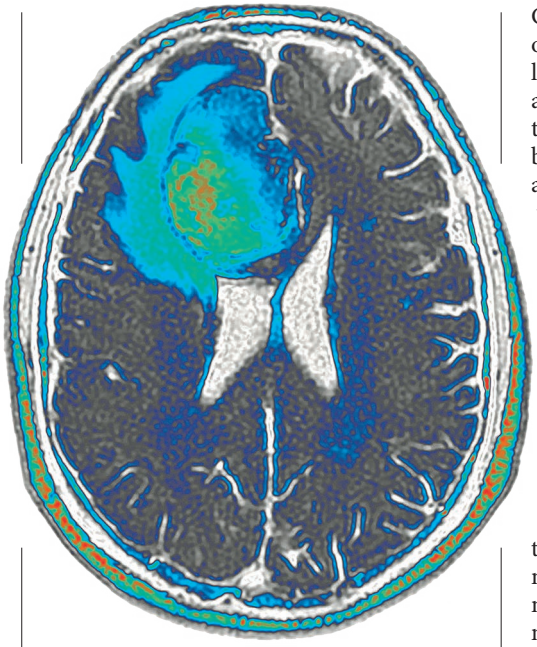
In April 2015, Barry Kappel left his job at a small anti-infectives firm, dug into the scientific literature and crossed his fingers. Kappel, who has a PhD in immunology and pharmacology from Weill Cornell Medicine in New York City, had long wanted to launch a biotechnology firm of his own. With enough savings to buy him 18 months, and 6 years of experience in business development, the time was ripe.

Over the next few months, Kappel read up on more than 100 research projects. A few dozen piqued his interest. He flew to Israel to check out some compelling drug candidates and cold-called potential partners from New York to California. By August, he had found what he was looking for just eight kilometres from his home — in the technology-transfer office at Columbia University in New York City.

"My mission was threefold," Kappel says. "I wanted a protein-based therapeutic that was 18–24 months from an investigational new drug filing with the US Food and Drug Administration and that would address a serious unmet need." The drug that ticked all three boxes was created by cell biologists Lloyd Greene, at Columbia, and James Angelastro, now at the University of California, Davis. The peptide-based therapeutic, which Kappel calls ST-36, kills cancer cells by inhibiting the transcription factor ATF5. If the drug makes it to the clinic, it will be transformative for people with glioblastoma — a brain cancer that kills up to 97% of patients within three years. ST-36 might also prove useful for other hard-to-treat cancers such as pancreatic and certain breast tumours.

Kappel founded Sapience Therapeutics in October 2015, and set out to raise money to optimize the drug candidate and validate the science behind it. Biotech founders often spend many gruelling months pitching their companies at roadshows in an effort to drum up interest from venture capitalists and institutional investors, but Kappel took a different approach for the bulk of his backing. He had the Merchant Capital division of the investment bank Maxim Group prepare a 120-page memorandum that summarized Sapience's business case and risks. The bank then sent this out to its clients. Investors used the report to decide whether they were interested. "I saved an unbelievable amount of time," says Kappel. This unconventional strategy was only possible because he had worked with the investment bank on a previous project, Kappel adds.

By July 2016, Sapience had raised US$22.5 million from investors.



MICHEL BRAUNER, ISM/SPL

Sapience Therapeutics is hoping to tackle the hard-to-treat cancer glioblastoma.

RISKY BUSINESS

One of the key backers of Sapience is the global biopharmaceutical company Celgene, which has an established cancer-drug pipeline. Columbia University's technology-transfer team had introduced Celgene to the drug candidate at the same time that Kappel was vetting the science. The company was interested in the protein's potential, but ultimately decided to reduce its exposure by backing Sapience to develop the therapeutic.

Kappel was more than willing to take on the series of uphill battles that start-ups must regularly endure. Drug researchers often categorize transcription factors as 'undruggable' targets. Inhibitors of these proteins have to reach the right cells in the right organs, and then penetrate the nucleus, where transcription factors help to convert DNA to RNA. These high barriers to entry limit the types of candidates that can be developed as therapeutics. And because transcription factors don't tend to have druggable pockets — sites that can be plugged up with small molecules — drug developers also have to work out how to block the notoriously intractable protein–protein and protein–nucleic-acid interactions that enable translation. "The soil has been salted by people who have failed," says John Lazo, a pharmacologist at the University of Virginia in Charlottesville, who was not involved with discovery of ST-36.

Rather than relying on a small molecule to block the activity of ATF5, Angelastro and Greene developed a non-functional version of ATF5 that binds to, and ties up, the cellular machinery of DNA transcription. They also tagged this biologic with a cell-penetrating peptide to smuggle it through the blood–brain barrier, into cancer cells and across the nuclear membrane. When they tested their candidate in mice, the gliomas were reduced or eradicated in all of the animals treated, and did not return in 12 months (C. C. Cates *et al. Oncotarget* **7**, 12718–12730; 2016).

"If this particular approach is as effective as the preclinical data suggest, then you could see a lot of other people saying maybe we should adopt the same strategy," says Lazo.

But that's a big 'if', he adds. Sapience will need to ensure that the drug is safe in toxicology studies. And the compound will need to be optimized to maximize efficacy, minimize side effects and make it easier to manufacture — a costly process for biological drugs. Nevertheless, Kappel hopes to file for regulatory approval to start clinical trials by the end of 2018.

This is why Angelastro's glad that the drug candidate is now in the hands of a start-up. "I had no idea that this project would go this far," he says, adding that his interest lies in formulating new hypotheses, rather than in toxicity screening and troubleshooting manufacturing processes.

"Sapience knows what they are doing," says Angelastro. "This way I can just focus on coming up with new ideas." ■

Asher Mullard *is a science journalist in Ottawa.*

CELLBRICKS

Building up from nothing

Technical University of Berlin

Building a 3D printer that can create living tissue and miniaturized organs was easy for Lutz Kloke, biologist and founder of biotechnology start-up Cellbricks. The tough part was finding the funding.

Investors in Germany "are quite risk-averse", says Kloke. "It's not like the US, where you can approach venture capitalists just having a prototype." He's had to go elsewhere to find funding for a pilot version of the printer and the cell-infused inks to go with it.

Cellbricks is developing 3D printers that create cubic-centimetre-sized biocompatible material laced with living cells. The material is made into models of human organs

DIRK HASSKARL/TISSUSE GMBH

Cellbricks uses 3D printers to create mini-organ systems that it hopes will speed up drug development.

that can be used for drug testing. The hope is that, because they behave more realistically than a 2D collection of cells in a petri dish, such organ-on-a-chip systems problems will detect problems earlier in the process, and thereby speed up drug development and cut costs.

"It's not like the US, where you can approach venture capitalists just having a prototype."

Unlike other bioprinters that extrude ink like toothpaste from a tube, Kloke's system uses stereolithography. Ink is exposed to a pattern of light using micromirrors; the ink hardens where the light hits, and the rest can be washed away. Kloke can use the patterning to create blood-vessel-like structures inside the printed object, allowing drugs and nutrients to flow through. His bioinks are based on materials such as collagen or hyaluronic acid, depending on the tissue type being printed.

Kloke won a €500,000 (US$534,000) grant from the German government's EXIST programme in 2015 after finishing his PhD at the Technical University of Berlin. The award is designed to help university researchers translate their work into a marketable product. "This basically helps to build a proper proof of principle and proof of concept, which investors can understand, and a business model which is working," he says. One of the requirements of the grant is that the researcher's university will provide the winner with a mentor, a workplace and free use of its facilities. Kloke's mentors are biotechnologists Roland Lauster and Uwe Marx, who is also chief executive of TissUse, another spin-off of the university that is developing an organ-on-a-chip system with a different type of technology.

Cellbricks will require more funding to begin full production of the printers, but the EXIST grant, and others that brought the total funding to €1.5 million, has allowed Kloke to hire employees and build the business. Cellbricks currently sells a pilot version to researchers for evaluation and is refining the system based on their feedback — a stage of development that could attract venture-capitalist investment. If it does, Kloke hopes that the company can grow beyond printing organs on chips to printing tissue for medical use. "In the long run, I want to create transplantable material," he says. "I think there will be transplantable material within the next decade." ■

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DENOVA SCIENCES

DENOVA SCIENCES
Clinical testing gets a new skin

Nanyang Technological University, Singapore

In Singapore, a young company is making waves with a new generation of tissue-engineered skin models and an accompanying set of research and development services. The company is poised to provide a much-needed combination of products plus services for organizations that require custom-made alternatives to animal testing in the production of cosmetics, pharmaceutical products and medical devices.

Following bans in the past few years on the use of animals for cosmetic testing in Europe as well as countries including India and Turkey, skin and wound-healing researchers Ming Jie Tan and Kelvin Han Chong Chung teamed up with entrepreneur Daniel Tan to create DeNova Sciences. The company has made models that mimic the characteristics of human skin, such as age, pigmentation and healthiness. The researchers grow the models in the lab from donated human skin cells.

"A lot of cosmetic companies have turned to *in vitro* model and human testing," says Ming Jie Tan, DeNova's chief scientific officer. "Those in Asia that do not have a research and development lab mostly seek companies in Europe for such services. We saw this gap."

DeNova was founded with 250,000 Singapore dollars (US$178,000) from private funds. The company received further funding, including a grant of $35,000 from the Singaporean government in 2014, and crowdsourced $140,000 in 2015.

The firm launched as a spin-off from Nanyang Technological University — where Ming Jie Tan and Chong completed their PhDs — in 2014, with a fully operational laboratory completed by the end of that year, says chief executive Daniel Tan. After a slow start, the company doubled its revenue in 2015 and then again in 2016 and is now profitable, he says. Its customers include cosmetic and pharmaceutical companies as well as governmental and academic institutions, he adds.

DeNova is aiming to distinguish itself from other companies that offer skin models, such as tissue-engineering firm MatTek and beauty giant L'Oréal, by providing an end-to-end service, from skin production to testing services and results analysis, says Ming Jie Tan.

The company's next goal is to gain validation from the European Union Reference Laboratory so that it can use its product as an alternative to animal testing. "It is important to get such validation to gain the confidence of both the clients and for a more-uniform method of testing for likewise, uniform results to be gathered," says Ming Jie Tan. ■

Karl Gruber *is a science writer in Perth, Australia.*

DeNova's skin model is used for product testing.