Credit: Colin Beatt

One year, 1 lab, 16 spinouts

In one year, George Church's group spun out 16 different startups. What explains the lab's incredible output of entrepreneurs?

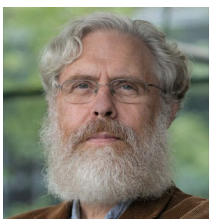
Laura DeFrancesco

In the early 2000s, Jay Shendure was a graduate student in George Church's lab at Harvard University. Back then, he says, there was "hardly an inkling" that the lab would become a hotbed of startup activity. Of course, licensing was ongoing, and Church had his tentacles into various companies, but there were only a smattering of ventures coming out of the lab — maybe one every year or so.

Fast forward to 2018, and the drip has turned into a deluge. Some 16 Church-cofounded companies came into being last year (Table 1). And several more added him to their scientific advisory boards (SABs). What explains the slew of ventures and incredible entrepreneurial output of Church's acolytes? Alumnus Dan Mandell of GRO Bioscience, a 2017 startup he spun out of the lab, puts it down to an 'esprit de corps': "We want everybody to succeed but we all know that the odds are not good for any particular biotech startup. All the cofounders share a delusional optimism." It's that optimism that keeps them going, he says. "It allows you to function in an environment where the odds are stacked against you but you somehow believe that you are going to make it work."

The secret sauce

Shendure feels the inflection point came in 2010, with the founding of AbVitro by Church and his then-postdoc Francois Vigneault. AbVitro may to this day hold a special place in the annals of startups from the Church lab. After starting from only a little over $3 million in startup funding from a single VC firm, Sante Ventures, in 2012, the company was snapped up by Juno for $125 million four years later. That was followed by Celgene's purchase of Juno, and more importantly led to several cell therapies now in



George Church, Harvard, MIT, Blavatnik Institute, Wyss Institute, Broad Institute, Regenesis Institute, Shenzhen Institutes of Advanced Technology and cofounder of 16 companies in 2018. Credit: Wyss Institute

Table 1 | Companies spun out of the Church lab in 2018

Company	Church alumnus and/or founder	Employees	Business focus
64-x	Alexis Rovner	5	Genome recoding
FitBiomics	Jonathan Scheiman	4	Microbiome therapy
Dyno Therapeutics	Eric Kelsic	16	AAV engineering
Kern Systems	Henry Lee	5	DNA data storage
Jura Bio	Julie Norville, Elizabeth Wood	2	CAR-T autoimmunity
GC Therapeutics	Parastoo Khoshakhlagh, Alex Ng	4.5	Cell therapies
Tenza	Anik Debnath	4	Secretory delivery
Nebula Genomics	Kamal Obbad, Dennis Grishin	14	Genomics
IXBio	Mike Chou		Transformative technologies
Calypso	Denitsa Milanova		Gene delivery via skin
Ally	Kai Chan		AAV immunity
Manifold Bio	Gleb Kuznetsov, Pierce Ogden		Protein engineering
NuProbe	David Zhang		Diagnostics
Rejuvenate Bio	Noah Davidsohn		Age reversal gene therapy
SNIPR Biome	Morton Sommer		Microbiome therapy
Feles	John Min		Lab-in-a-box

Source: George Church

the investigational new drug (IND) phase, according to Vigneault. "[Church] never had a really big success until we decided to do AbVitro and that one ended up knocking it out of the ball park. That triggered a lot of people to start companies because it looks easy from the outside," he says. "It's not," he adds.

Whether or not AbVitro was the bellwether, the pace began picking up around 2015, and reached a fevered pitch in 2018 (Fig. 1).

That year's rich vintage of ventures come in all shapes and sizes. Most are working with pre-seed or seed funding, but a couple have garnered VC funding. A few have a decent sized team of a dozen or so, whereas others are operating with only a founder or two, who are doing it all. Several have set up shop side by side in one of the incubators in Cambridge, where they share not only core facilities but also war stories.

According to Grant Zimmermann, managing director of business development at Harvard's Office of Technology Development (OTD), the biggest change from the past is that lab members are stepping up to take the role of CEO, rather than chief scientific officer (CSO) or chief technology officer (CTO). He sees an upswing in entrepreneurial verve across the university, but especially coming out of the Church lab. "They really have a desire to take on that business challenge of managing the company and growing the opportunity, seeking out the financing, seeking out the collaborations, and really focusing on the business aspect," Zimmerman says.

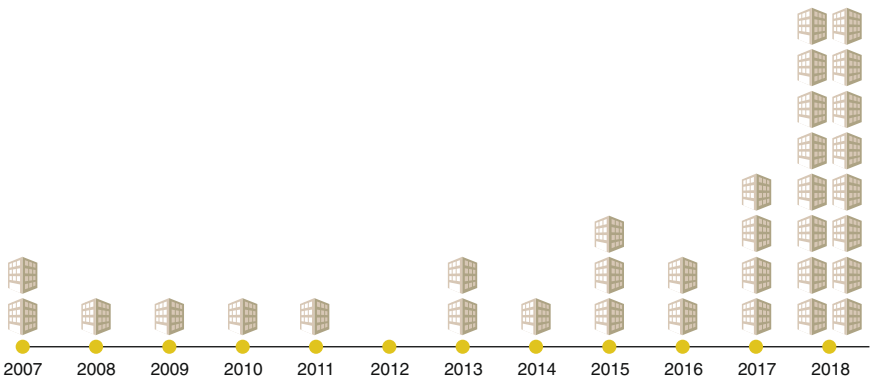


Fig. 1 | Timeline of 'newcos' from the Church laboratory. Source: George Church.

It is not without its personal risks for the founders, but the cadre has plenty of support both from within the Church lab and its network of successful entrepreneur–alumni, and from the commercial ecosystem around Cambridge. The OTD office brings in mentors to work with aspiring CEOs. And, as for other investigators at Harvard and its sister institution the Wyss Institute, various accelerator and incubator programs provide money and lab space, grooming researchers for success.

Starting off small

It doesn't always take millions of dollars to form a biotech startup. For Julie Norville, a former postdoc in the Church lab, it took just an idea. She saw a real-world problem and, in the true Churchian spirit, set about solving it. A friend of hers was in need of an organ transplant, and Norville worried about the ordeal her friend would encounter and the steroid immune suppressants she would be dependent on. As a response, she founded Jura Bio with a fellow former MITer, Elizabeth Wood, based on an idea for engineering chimeric

Julie Norville, cofounder and co-managing director, Jura Bio. Credit: Ryuji Suzuki

Elizabeth Wood, cofounder and co-managing director, Jura Bio. Credit: Ryuji Suzuki

antigen receptor (CAR)-T cells to treat autoimmunity (rather than cancer). She floated the idea by her former mentor, Church, who encouraged her to go with it, with the added bonus of signing on as a cofounder. Now, roughly a year later, Norville and Wood are still a company of two, but have shelved the program focusing on immune rejection to tackle more tractable single-epitope autoimmune conditions. They have devised a 'decoy' using the human major histocompatibility complex (MHC) to target both T and B cells, which expands potential targets and makes for better binding, according to Wood. The company is currently engaged in raising additional fund.

Alexis Rovner, cofounder and CEO, 64-x. Credit: Alexis Rovner

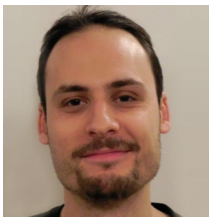
Alexis Rovner, CEO of 64-x, is also running her company lean. She says this is possible because of the relative ease of doing experiments with the synthetic biology platforms now available. "Basically you are able to invent technology around problems easily, that's just what is motivating scientists to spin their tech out into some kind of company. Before, it wasn't this easy to engineer biology. It's getting easier, the tools are easier, the things we are able to do to cells — it's amazing what's now available," she says. Rovner was a student at Yale University with Farren Isaacs (himself a former postdoc from the Church lab), working on a technology for recoding organisms, an area of intense interest to Church. A collaboration between the two labs led to Rovner's joining the Church lab as a postdoc. At that point, her only interest was in developing the technology wherever, in academia or in industry, but she eventually opted for industry. To learn how to do that, she did a stint at Y Combinator in the San Francisco Bay Area, which provides space and resources for budding CEOs to learn the basics of starting a company. Three months later, Rovner returned to Cambridge with a small seed fund and the tools she felt she needed to go forward. She credits Church with giving her not only the space to develop the technology but also the time to allow her passion to gel. "Once I realized that I wanted to more of the applied side of trying to commercialize science, it takes a leap of confidence to do it. I feel that George gave me that confidence. That's the power of the Church lab, to be honest," she says.

Henry Lee, cofounder and CEO, Kern Systems. Credit: Aiden Rhaa

Y Combinator support is factoring into another one of the 2018 startup cohort, Kern Systems, headed up by Henry Lee, who joined the Church lab as a postdoc in 2012. Trained as an electrical engineer, Lee came to the area to learn some biology, starting in Jim Collins' lab, which was then at Boston University. Given his background in electrical engineering, the way Collins framed genes and cells as circuits "spoke to him," says Lee. But another aspect of being an engineer is addressing real-world problems; he moved to the Church lab to work on a technology for reading and writing DNA at scale. Together they developed a method for enzymatic synthesis of DNA, an essential but still lagging technology, for the 'DNA-Write' sector of the synthetic biology movement. This technology forms the basis of Kern Systems, which, in addition to support from Y Combinator, has received grants from and worked in partnership with Technicolor Research and Innovation Lab. Lee echoes Rovner's sentiment in seeing a shift coming, where biology is getting to the point where you can do "bite-size events" with a shoestring budget. "We don't have to go through the long rigid process where there is only one way to assess progress. That's been fantastic, has provided a lot of opportunities for young ambitious scientists to really go out there and make an impact," he says.

Hoop (and other) dreams

What many founders have in common is a vision or a dream, and the Church lab appears to be a place where people are given space to follow their dreams. For Jonathan Scheiman, CEO of FitBiomics, it was his hoop dreams — he had contemplated a career in the NBA after playing on a two championship basketball teams at St. John's University in the early 2000s. But when he joined the Church lab as a postdoc, he came to explore cutting-edge technologies, fresh from a thesis in molecular oncology. During his initial meeting with Church, his intense



Jonathan Scheiman, cofounder and CEO, FitBiomics. Credit: FitBiomics

interest in athletics came up, to which Church responded, "That's good! We want people who think differently." After contributing to various projects ongoing in the lab, Scheiman came up the hook that would become the basis for FitBiomics, a venture looking at the microbiomes of elite athletes. "What if instead of looking at diseased populations, we looked at super-fit or healthy people and see what is unique or enriched in them. Can we identify a molecular component that drives optimal fitness?", he wondered. This did not come totally out of left field; there were people already engineering microbes and microbiome communities to do various things. Scheiman's idea of working with elite athletes led to a *Nature Medicine* paper (*Nat. Med.* **25**, 1104–1109, 2019), coverage in pretty much all the major news outlets, and a company. He says coverage was almost automatic; he only had to "mention three things: microbiome, athletes and George Church." Now back in his beloved Manhattan, ensconced in BioLabs New York, an incubator in trendy TriBeCa, Scheinman and a small crew of experienced advisors are looking for funding.

Anik Debnath, cofounder and CEO, Tenza. Credit: Mariah Torpey

Anik Debnath, CEO of Tenza, had no thoughts of starting a company when he joined the Church lab in 2103, but he, too, had a dream — to engineer the vaginal microbiome to deliver a prophylactic HIV vaccine. He came up with this idea from his observing work on prophylactic vaccines going on at Caltech when he was an undergrad there, and from his exposure to clinical problems while participating in a special program at Harvard that provides PhD candidates with clinical experience. Even though he was only beginning his graduate work, Church allowed him to pursue this idea. There was nothing quite like it going on in the lab, but what was there were many experienced researchers who could guide Debnath, a physics major with no prior lab experience, around the lab. "I was starting at zero, total lack of

experience with molecular biology. I was taught everything I knew from the postdocs I was sitting with. Even though I was alone in building this project, at the same time, I wasn't," he says. Ultimately, Debnath's vision of a vaginal-microbiome-based vaccine was set aside — the bacterial strains were difficult to work with — but he was inspired to pursue the wider application of using the microbiome as a delivery vehicle. Debnath stayed on as a postdoc to flesh out this idea, but eventually it came time to take it out of the lab. With a modest budget derived from private investors and from winning several startup competitions, Debnath founded Tenza with a team of four people, all, like himself, willing to work at what he calls postdoc-level wages. The group has set its sights on targeting large needs like inflammatory bowel disease.

Alex Ng, cofounder and CSO, GC Therapeutics. Credit: Parastoo Khoshakhlagh

Parastoo Khoshakhlagh, cofounder and CEO, GC Therapeutics. Credit: Alex Ng

The lure of cutting-edge science in the Church lab is also what brought Alex Ng there for his graduate studies. In the group, he says, "You feel like you are bringing science fiction into reality but in a meaningful way." Church was the catalyst in connecting Ng with Parastoo Khoshakhlagh, a biomedical engineer who at the time was a postdoc at the Wyss. Khoshakhlagh had had the experience of developing an organ-on-a-chip technology using neural stem cells, which was licensed out to neurotech biotech AxoSim, and had been CSO of an all-women startup, Tympanogen, which developed a patch to repair ruptured ear drums. When she joined the lab, Church teamed her up with Ng on his thesis problem, which they then turned into the foundation for GC Therapeutics. They have created a platform exploiting thousands of human transcription factors (the 'TFome', encoded by >1,500 genes) to create reprogramming cocktails capable of differentiating human pluripotent stem cells into potentially any desired type of mature cell type — a system Ng claims has higher yields and is much faster than most other differentiation methods. Although they initially found the idea a hard sell to investors (who have since come around), companies immediately understood the power of the platform. "Already eight companies are knocking on our door to make sure they have a hand in this," says Khoshakhlagh. And the local innovation ecosystem has stepped up and provided seed funding; the pair were accepted into several local competitions, winning a couple that were enough to launch the company. They also received support from both the Wyss Institute and the Harvard Blavatnik Accelerator, maintaining their ties to Harvard while they de-risk the technology and build their team. Of Church, Ng says, "He wants to have people with different skill sets with different things to bring to the table and a mindset open to commercialization and entrepreneurship."

Eric Kelsic, cofounder and CEO, Dyno Therapeutics. Credit: Dyno Therapeutics/ Sam Sinai

Going big

Like Debnath, Erik Kelsic, CEO of Dyno Therapeutics, had no thoughts of starting a company when he started graduate school at Harvard. "I started grad school thinking I was on the academic track," he says. His graduate project, on multiplexing reading DNA sequences, intersected with technology being developed in the Church lab, specifically multiplex automated genomic engineering, or MAGE. "Multiplexing [is] George's favorite thing. Everything he does, he does by multiplexing," he says (on a recent podcast, Church said that "multiplexing should be my middle name"). In fact, Kelsic worked on a technology called MAGE-seq as part of his thesis, so Church was a natural fit for his doctoral committee as well as for a postdoctoral mentor. As Kelsic was working on his degree, he also helped a friend develop pitches for business-plan competitions, and this is where he caught the startup bug. In the Church lab, Kelsic led a team that took on the challenge of designing adeno-associated viral (AAV) vectors for protein delivery by marrying three technologies — DNA synthesis, sequencing and machine language (recently published: Ogden et al. *Science* **366**, 1139–1143, 2019). The group intuited the gene therapy community's appetite for better vectors, and after being granted seed funding from Harvard and the Wyss, set up the nascent company in the Cambridge incubator LabCentral, starting with one bench, but quickly getting the attention of local VCs who have provided funding that enabled them to move up into a private suite with 16 full-time staff. Kelsic sums up his time in the Church lab this way: "What's unique… is that George is supportive of doing projects where a startup is the end goal. I was able to think about that from the very beginning, which is different from the way things go at most universities. You think about a company at the very end."

Kamal Obbad, cofounder and CEO, Nebula Genomics. Credit: Anthem Multimedia

Nebula Genomics has also amassed a respectably sized group in a short period of time — 14 people in two locations. This company, which created a secure environment for sharing and storing genomic information, may at last succeed at something Church has been trying to do for decades. In 2007, he set up a venture called Knome to sequence individual genomes (for a considerable sum of money). Although this business never really took off, the nonprofit 'Personal Genomics Project' — a free and totally accessible database of individuals' health data, including genomes — followed and was more successful. The new idea for Nebula (*Nat. Biotechnol.* **37**, 1115–1117, 2019) came from now-CEO Kamal Obbad, who was at Google when he contacted Church with the idea of creating a blockchain for sharing sensitive genomic information. He barely had gotten out the word "blockchain" when Church chimed in that he had been mulling over the same idea, and had a student in his lab, Dennis Grishin, who was a perfect partner for Obbad. After only a couple of years at Google, Obbad was ready to move on, and he lived on his savings for six months while the trio crafted the Nebula platform. It has paid off; they have already raised a series A round from no fewer than 12 investors and established a partnership with a major pharmaceutical company, and are now raising revenues from people using the platform. Church has taken an interest in the company, and it's paid off. "George is a great way to get the flywheel started and to get a big respected experienced name involved with your company. At the end of the day, the business needs to have solid footing for VCs to get interested," says Obbad. Being part of the Church ecosystem helps too, as Church

encourages his companies to work together. "We do genetic testing, we can work with companies, creating new sequencing technologies, giving us access to cheaper platforms. There's a lot of interesting things that you can do with Church lab ecosystem that has proved valuable."

New world order

Church has worked on the cutting edge of technologies for decades, yet in recent years, activity coming out of his lab has reached a fevered pitch. According to his long-time friend and collaborator Jorge Conde, who back in 2007 cofounded Knome, one of the few failed Church enterprises, the current startup environment is different from that of the past in several significant ways. There is a very rich ecosystem of infrastructure for startups to launch into. "Places like LabCentral or Alexandria LaunchLabs are where you have a full BSL2 [biosafety level 2] lab ready to go and you can rent a bench on and have access to equipment for relatively small amounts of money," he says. Access to capital is high for these kinds of ventures, he says, adding that a new breed of scientific founder is also emerging. "They have grown up in the era of startups, and have technology, multidisciplinary backgrounds across biology, computer science and engineering," he points out.

In addition, the technology may now be catching up with some of the Church "crazy" ideas of years past. Cain McCleary, of KdT Ventures, which has invested in two from this cohort and one a few years back, says, "I feel like he's consistently been ahead of his time in creating tool sets, but all of a sudden, our analysis and manufacturing has caught up to it, so it's a particularly special time for folks in his lab," he says.

Church himself doesn't pretend to know why 2018 was such a productive year, but he says that there is a positive feedback loop, dating back to the founding of AbVitro, which had a nice exit, and the recent startup by Luhan Yang, eGenesis Bio, which had a nice entrance, with an A round of $39 million in 2017, followed by a $100 million B round in late 2019. There's also a mass affect. The Church lab has one of the highest densities of people at Harvard. "Having all the crazy interdisciplinary people in the same lab — there's something to be said for high concentration. People bounce around ideas more when they are close to each other," he says. Zimmerman would agree. "Church has an amazing number of innovative teams in his orbit. It creates a gravity that pulls in like-minded people," he says.

Conde sums up the current situation with his former mentor: "My sense is what he does is to try experiments and see what works and doesn't work. By spinning out companies, he's running a social experiment to see if an idea is better served in academia or industry. He's certainly not afraid of failure."

In fact, Church himself sees failure as an important component of his success. "A lot of people reject ideas without even trying them. Other people will try them and then throw them in the trash. We put them up on the wall and glorify our failures as challenges for the future. If you're not failing, you're not trying," he says.

For a complete transcript of a conversation with George Church, go to our Bioengineering Community *page.* ❐

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