ToughTech

A publication by The Engine, built by MIT

FALL 2018

Tough Tech Summit Recap | New Lease On Life | The New World Of New Space

We asked attendees of the inaugural Tough Tech Summit what "Tough Tech" means to them. These are some of their responses.

"Tough Tech means tackling the problems of tomorrow, today." | "It's resource-intensive to bring to market but worthwhile pursuing for its transformative value to humanity." | *"It's tech and VC at their most ambitious."* | "It's thinking about problems first, and profits second." | *"It's about addressing the challenges that must be met, rather than those that are easy to solve."* | "It's harder, it can take longer, but the payoffs are higher." | *"It's an insatiable desire to design solutions to seemingly impossible problems."* | "Unapologetic persistence. It's a moonshot based in deep societal need." | *"It's fundamental innovation, yielding significant, game-changing breakthroughs."* | "Technology + untraditional thinking." | *"Changing the vector of society."* | "Something so far off that it initially lives on a paper napkin at a café, where at the time the sketch seems absurd." | *"When you say your start-up can change the world, it's not an exaggeration."* | "High tech, high risk, world-changing rewards." | *"Tangible technologies, often steeped in material science innovations, to solve long-term real-world problems."* | "Take the estimated time and money to develop and commercialize the technology and multiply them both by Pi."

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Tough Tech Publication 02

Fall 2018
The Engine, Built by MIT
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A home for Tough Tech founders.

The Engine, built by MIT, is a home for Tough Tech founders building the next generation of world-changing companies.

We fulfill our mission through a mix of long-term capital, access to specialized infrastructure and facilities, and the platform to collaborate and learn from a network of founders, investors, academics, and corporations.

We invest in founders who are working on scientific breakthroughs and converging technologies that hold the potential to change the future.

From Tough Tech Moment to Tough Tech Movement

When we founded The Engine, we had two goals. The first was to invest in and work with founders creating the scientific breakthroughs and converging technologies that hold the potential to change the future. The second was to convene those who wanted to collaborate in helping these founders solve society's most important problems.

Today, both are happening.

We have a portfolio of 14 founder-led companies and a network including 23 other Tough Tech startups. We are seeing industry, academia, investors, entrepreneurs, and government leaning in—recognizing that our collective future rests with these founders.

We've seen, first hand, the desire for Tough Tech. Collectively, as an ecosystem, it's our job to help founders in any way we can. To say yes. To help them learn and thrive. Because if we do, we all win.

Katie Rae
CEO & Managing Partner, The Engine

Photos by *Jake Belcher*

Why Tough Tech Matters

It was Rafael Reif, the President of MIT, who, in 2015, first suggested the idea of an innovation orchard to provide "physical space, mentorship, and bridge-funding for entrepreneurs"—the seed of which would become The Engine. He, along with Katie Rae, The Engine's CEO & Managing Director, kicked off the Summit, reflecting upon the intersections between academia, venture capital, strategic corporate partners, and government.

Hans Peter Brøndmo continued the conversation with stories, data, and lessons focused on a Tough Tech company's human element, reminding the audience that intentionally creating a culture of audacity helps inspire the novel thinking that can solve our toughest problems. Sue Siegel concluded the keynote session with perspectives on how one of the world's largest corporations can help foster Tough Tech innovation at scale using lessons from its past.

THE ROLE OF INVESTORS

Katie Rae

CEO and Managing Partner, The Engine

"The Engine follows the lead of our founders. Their vision of the future is born out of deep research and knowledge about how the world should look. They've spent years if not decades to bring the technology to the point that it is ready to commercialize, and they are dedicated and motivated to face the challenges to make it a reality. They are on a mission."

THE ROLE OF ACADEMIA

L. Rafael Reif

President of Massachusetts Institute of Technology

"Research universities bring together talented people from around the world. And they empower them by providing the expertise, experience, and resources they need to innovate … and deliver their solutions to society. That is the role of academia in the Tough Tech movement."

"We believe in the tremendous potential that Tough Tech has to do good in the world."

THE ROLE OF TALENT

Hans Peter Brøndmo

Robotics Project Lead, X,
The Moonshot Factory (formerly Google [x])

"New ways of thinking about old problems—that's what Tough Tech is all about."

"Start with just a vague inkling that it may be possible."

"Fall in love with the problem, not the technology."

"Take it to the real world early."
"Stay curious and humble."

THE ROLE OF CORPORATES

Sue Siegel

Chief Innovation Officer,
GE and CEO of Business Innovations

"The pace of change will never be as slow as it is today."

"I've learned that [Tough Tech] is one of the most inspiring things that you can do."

"Tough Tech is not about financing and technology alone, it's the ecosystem that has to be developed."

"Working in partnerships does not come easy to those that **could** before, to those that **didn't have to** before."

Tough Tech Summit by the Numbers

Tough Tech Summit[SM]
10.29.2018. Boston.

366 Attendees

135 Founders

29 Investors

29 Speakers

27 Corporate Leaders

20 Academic Leaders

3 MORNING TRACKS IN PARALLEL

BEV Lunch
1 Breakthrough Energy Ventures Lunch Session

3 AFTERNOON TRACKS IN PARALLEL

9 Keynote Speakers

31 Tough Tech Startups Posters

CONFIRM COMPLICATE
450 Confirm & Complicate Paddles

1 Tough Tech Summit Partner

3 Tough Tech Summit Sponsors

Breakthrough Energy

MINTZ

BASF We create chemistry

WilmerHale

22 Tabletop Succulents

15 Palm Trees

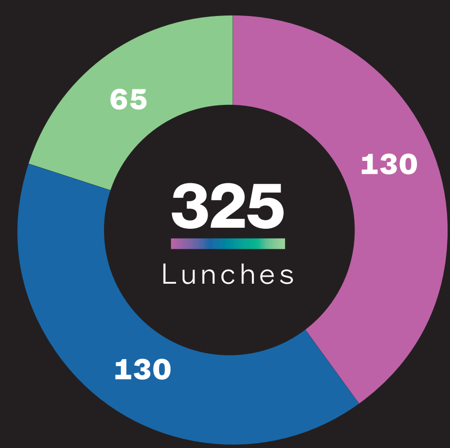
1 Column Sculpture

4 10,000 Lumen laser projectors

6 CatchBox mics

9 75˝LCD Monitors

28 Wireless Microphones



Turkey sanwiches

Prosciutto sanwiches

Salads

Beers

Bottles of wine

3 The Engine Network Strategic Corporate Members

37 The Engine Network Tough Tech Startups

EVONIK POWER TO CREATE

GE

HYUNDAI CRADLE

Company Building

Tough Tech leaders moderated hands-on sessions focused on managing the complex transition to market, including funding, leadership, and strategic partnerships.

A — Funding Tough Tech At Every Stage

Carmichael Roberts | Moderator
Member, Breakthrough Energy Ventures
Katie Rae
CEO & Managing Partner, The Engine
James Zahler
Associate Director for Technology-to-Market, ARPA-E
Dayna Grayson
Partner, New Enterprise Associates
Daniel Hullah
Managing Director, GE Ventures

Takeaways

Family offices and high-net-worth individuals have high alignment, in particular, with Tough Tech—entrepreneurs take note: these segments are critical components of the funding ecosystem.

The presumed capital intensity of Tough Tech makes small investors uncomfortable. But it is important to note that not all deals require massive amounts of capital. It's imperative that larger investors make the importance of smaller investors known.

"The notion of chasing early returns in software is tired. There is massive opportunity in Tough Tech. The competitive sets are smaller, and markets are bigger. All venture capital firms need to lean in to Tough Tech."

"Paying attention to the consumer is important, even though that's not always in the main corporation strategy. Every business ends with C, even if it is a B2B."

B — Building and Nurturing Successful Strategic Partnerships

Ann DeWitt | Moderator
COO & General Partner, The Engine
Bob Mumgaard
Co-Founder & CEO, Commonwealth Fusion Systems
Mick Mountz
Founder & CEO, Kiva Systems
Charlie Purtell
VP New Ventures, Danaher Life Science Innovation Center
Russ Wilcox
Partner, Pillar; Former Co-Founder & CEO, E Ink
Iya Khalil
Co-Founder & Chief Commercial Officer, GNS Healthcare
Dave Gammell
Partner, WilmerHale

Takeaways

"Your strategic partner most often ends up shaping the way you build your product and your company. Nurturing such a relationship at all levels is paramount."

"Ask why. Then shut up and listen."

On negotiations: set principles and goals internally, then look for alignment of business interests and those goals.

A deal is a dynamic process, pace yourself and your concessions. Don't be afraid to play the startup card.

C — Transforming Academic Leaders into Leaders in Business

Ilan Gur | Moderator
Founder & Executive Director, Cyclotron Road
Nabiha Saklayen
Co-Founder & CEO, Cellino
Bilal Zuberi
Partner, Lux Capital
Raymond Weitekamp
Founder & CEO, polySpectra
Yet-Ming Chiang
Kyocera Professor of Materials Science and Engineering, MIT, Co-Founder, Form Energy

Takeaways

There is usually a "crisis moment" that catalyzes the transition of an academic into a business leader. A certain level of self-awareness helps navigate what can be a humbling transition.

Founders should be dreamers, not realists. They should sell their vision. After all, most startups fail due to reasons other than their technology.

"Why are you the right person to tackle this problem? The answer can't be 'because I was the grad student that invented this.' The answer has to be 'because I'm the right person to pull together all the resources.'"

"It's about problem definition before technology definition."

Technology & Product Strategy Case Studies

Founders presented case studies of pivotal moments within their own companies, fostering an honest and productive dialogue about the challenges of building, scaling, and operating a Tough Tech company.

X — Supply Chain Strategy and Its Effects on Commercialization

Kevin Munnelly
Executive in Residence, Biological Engineering Ventures
Sean LeBlanc
Director, DNA Synthesis Operations, Ginkgo Bioworks
Libby Wayman | **Facilitator**
Breakthrough Energy Ventures

Takeaways

Supply chain strategy must be a part of a founder's business strategy as early as possible.

Founders should not think of corporate partners as slow and predictable—many of these companies may be in flux. Such unpredictability can affect a partnership and operating behavior in unexpected ways.

"Allocating the resources to fix an unsound supply chain strategy can run into the 10s of millions of dollars. Redoing this work could spell the end of the venture."

"Founders should seek out supply chain advisors with diverse opinions and different areas of expertise."

Y — Managing the Tension Between R&D and Market Demands

David Bradwell
Co-founder and CTO, Ambri
Michael Kearney
MIT Sloan School of Management
Reed Sturtevant | **Facilitator**
General Partner, The Engine

Takeaways

In an effort to de risk the market, founders often have to make suboptimal choices related to technology development.

Founders need to be aware of the intrinsic trade-offs and balance the relative value of de risking the market with the relative value of de risking the technology.

Investors should be aware of these trade-offs, as well, and ensure that founders are not pursuing sub-optimal paths simply because of perceived pressure from the investment community.

"Market choices don't happen in a vacuum, your technology trajectory is fundamentally dependent on the market you select."

"So many technologists have to deal with the challenging question of at what size they should scale their technology."

Z — Strategies That Inform a Successful Product/Market Fit

Stan Lapidus
Managing Director, Lapidx Research
Theresa Tribble
Chief Business Officer, EverlyWell
Ann DeWitt | **Facilitator**
COO & General Partner, The Engine

Takeaways

Determining an appropriate product / market fit is easy, if you listen. Founders should speak to the consumers of their product without selling anything, just listen and ask questions.

Start with data, make a hypothesis on early customers, define the product, make sure that fits the market. This can be a messy process.

Define when to "kill", "improve", "launch". If not, it's too easy to convince yourself that the data is good enough.

"Sometimes you think you have a product and you think you have a market, but you really don't have either."







Breakthrough Energy Lunch Session

Breakthrough Energy shared its model of linking government-funded research with risk-tolerant capital to bring clean energy innovations to market faster. This introduction was followed by a discussion of the challenges associated with providing reliable electricity, healthy food, durable goods, comfortable buildings, and convenient transportation to everyone on the planet without contributing to climate change.










Perspectives from Five Tough Tech Founders

Three industry veterans and two of Tough Tech's brightest rising stars, these five founders shared candid moments, lessons, and perspectives from their respective journeys as founders of Tough Tech companies.

Ric Fulop

CEO & Founder, Desktop Metal

"Businesses that have a single or small number of customers are not good for venture returns. You have the consolidation of pricing power in the hands of few people. You want to work on products that have lots of customers."

"It's all about people and team building. My management team has built their own teams—try to build a team of people who can create outsized returns, then they hire like that."

Tillman Gerngross

Professor of Bioengineering at Dartmouth College; Co-Founder & CEO, Adimab

"Every company is a hypothesis that requires capital to test. And by the way, that capital has an opinion."

"If you do what everyone else does, you shouldn't expect any different outcome."

"At some point in the lifecycle of your company, this becomes true: market value $\sum$ good decisions dv - $\sum$ bad decisions dv."

Natalya Bailey

Co-Founder & CEO, Accion Systems

"Almost everything you do at an early-stage company will be a negotiation, sale, or both. These are skills you can learn and get good at. And they will be relevant to your time as a startup executive."

"The theme that's been true for me [as a founder], and perhaps for the technical folks coming from labs, is that people have been the hardest part. Not the technology itself."

"Whether you're a PhD student or a startup founder, you have to believe that the world truly needs your solution, and if you're not going to do it, than somebody else will because the need is so real and powerful."

Jason Kelly

CEO, Ginkgo Bioworks

"Tough Tech that could be the basis for successful corporations is abundant. The challenge is that Tough Tech requires deep, specialized knowledge. The reality is, you've got to know what the hell is going on."

"To me, the only example of functioning early-stage hard tech capital is in pharmaceuticals."

"Don't be afraid of government funding."

"How to solve the missing early capital in Tough Tech? Hustle. Enable non-specialists to invest before technical de-risking with other validation."

Danny Hillis

Co-Founder, Applied Invention

"Anybody who undertakes one of these Tough Tech problems is really, in some sense, doing something foolish. There are much easier ways to make money. But it turns out that the things that really change the world are those tough things. Even though it's kind of crazy, and even though you're likely to fail, those are the only things worth trying for."

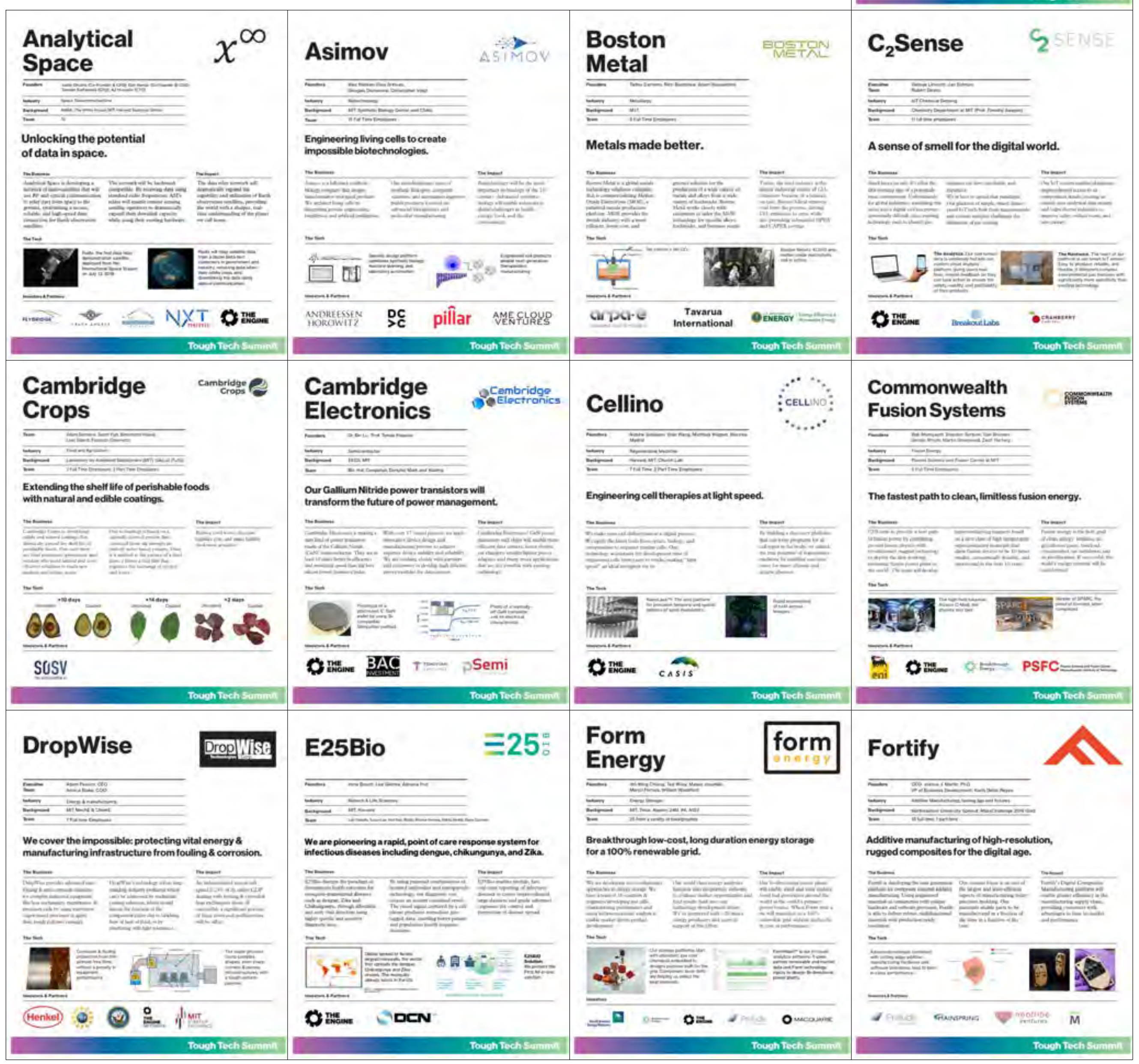
"I learn more from things that don't work out."

"The time you're least paying attention to cash, is the time you're most vulnerable for it. The lesson: have more cash than you think you need, especially if business is growing rapidly."

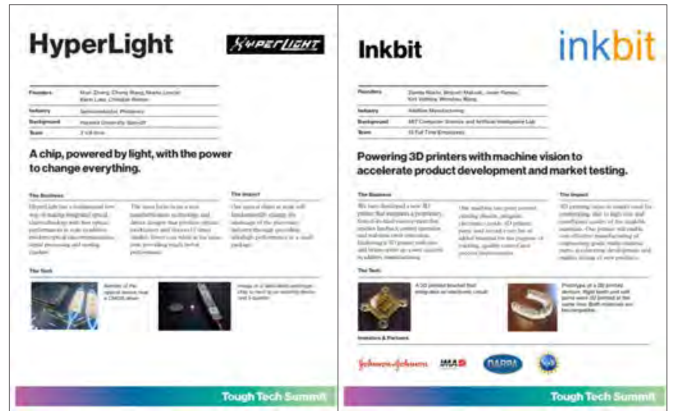
"Tough problems attract great people, who continue to thrive and work together."

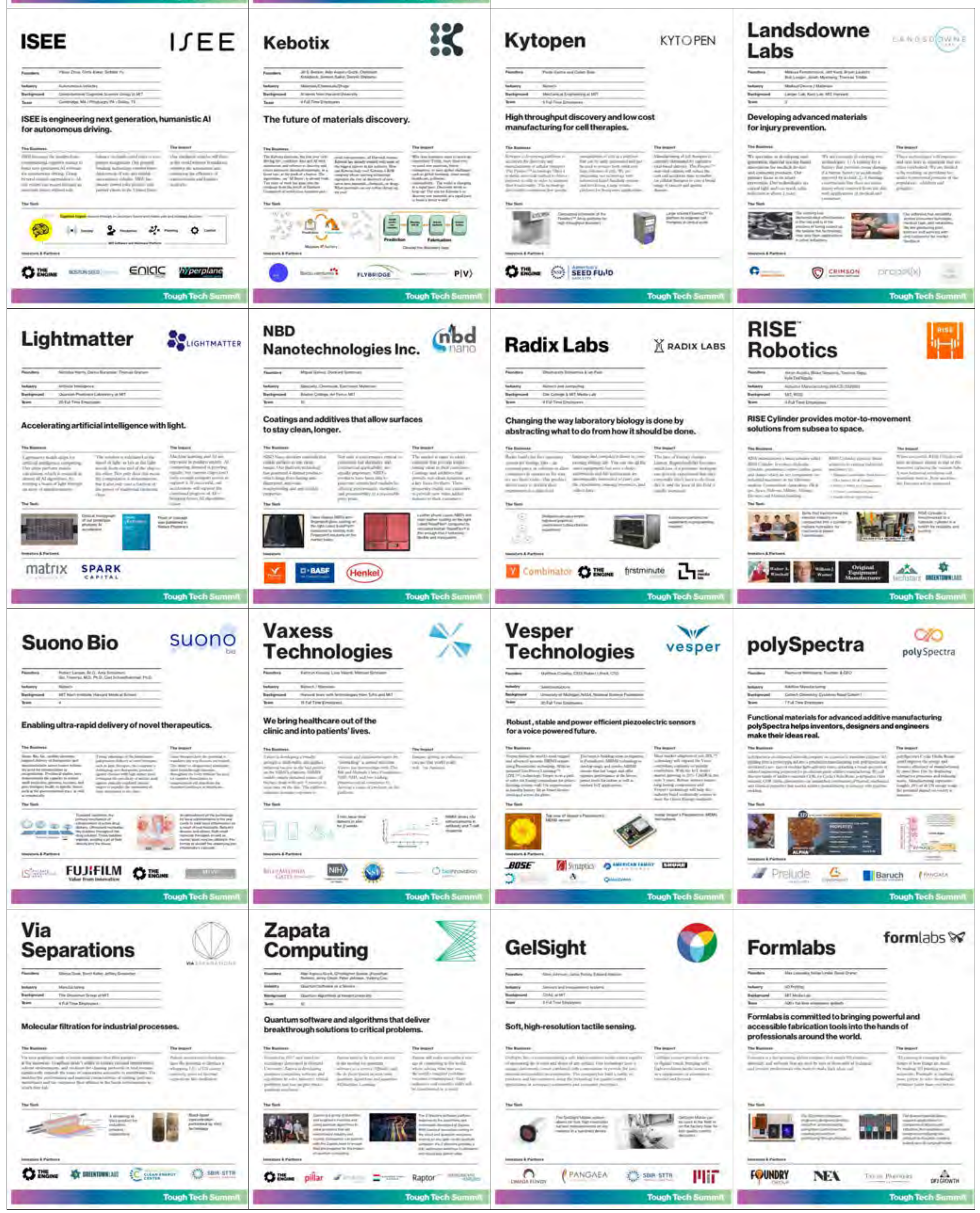
Connecting with Tough Tech Startups

These posters, featuring Tough Tech startups within The Engine Network, were displayed in the hallways of the Tough Tech Summit. Attendees could mingle, meet the companies, and learn about their science, technology, and impact.



Tough Tech Summit℠
10.29.2018. Boston.





THE ENGINE NETWORK

The Engine Network is driven to build long-term, mutually beneficial relationships between Tough Tech startups and strategic corporate members, in turn helping create and sustain a Tough Tech movement throughout the region.

October 28, 2018 marked the formal kickoff of The Engine Network with a gathering at The Engine in Cambridge, MA. Both founders and corporates participated in roundtable discussions and an “ask / offer” exercise. Network members left the evening with new relationships, productive insights, and actionable paths forward.

Tough Tech Strategic Corporate Members

(as of November 2018)

Evonik — Power to Create

GE

Hyundai Cradle

Tough Tech Startups

(as of November 2018)

- Accion Systems
- Ambri
- Analytical Space
- Asimov
- Boston Metal
- C2Sense
- Cambridge Crops
- Cambridge Electronics
- Cellino
- Commonwealth Fusion Systems
- DOTS
- DropWise
- E25Bio
- FemtoDx
- Form Energy
- Formlabs
- Fortify
- Gelsight
- Hyalex
- HyperLight
- Inkbit
- ISEE
- Kebotix
- Kytopen
- Landsdowne Labs
- LECT
- Lightmatter
- Metalenz
- NBD Nano
- Portal Instruments
- Radix Labs
- RISE Robotics
- Suono Bio
- Vaxess
- Vesper
- Via Separations
- Zapata Computing

Tough Tech Summit℠
10.29.2018. Boston.

The Tough Tech Summit was never intended to forge some tidy solution to solving the big problems. It was designed to convene. To unite the brightest minds, the most visionary thinkers, and the most experienced entrepreneurs so that they could hear from each other, put faces to names, and get the conversation started. That it did.

As Hans Peter Brøndmo remarked in his keynote, “We have just a vague inkling of what may be possible.” And that’s the most exciting thing of all.

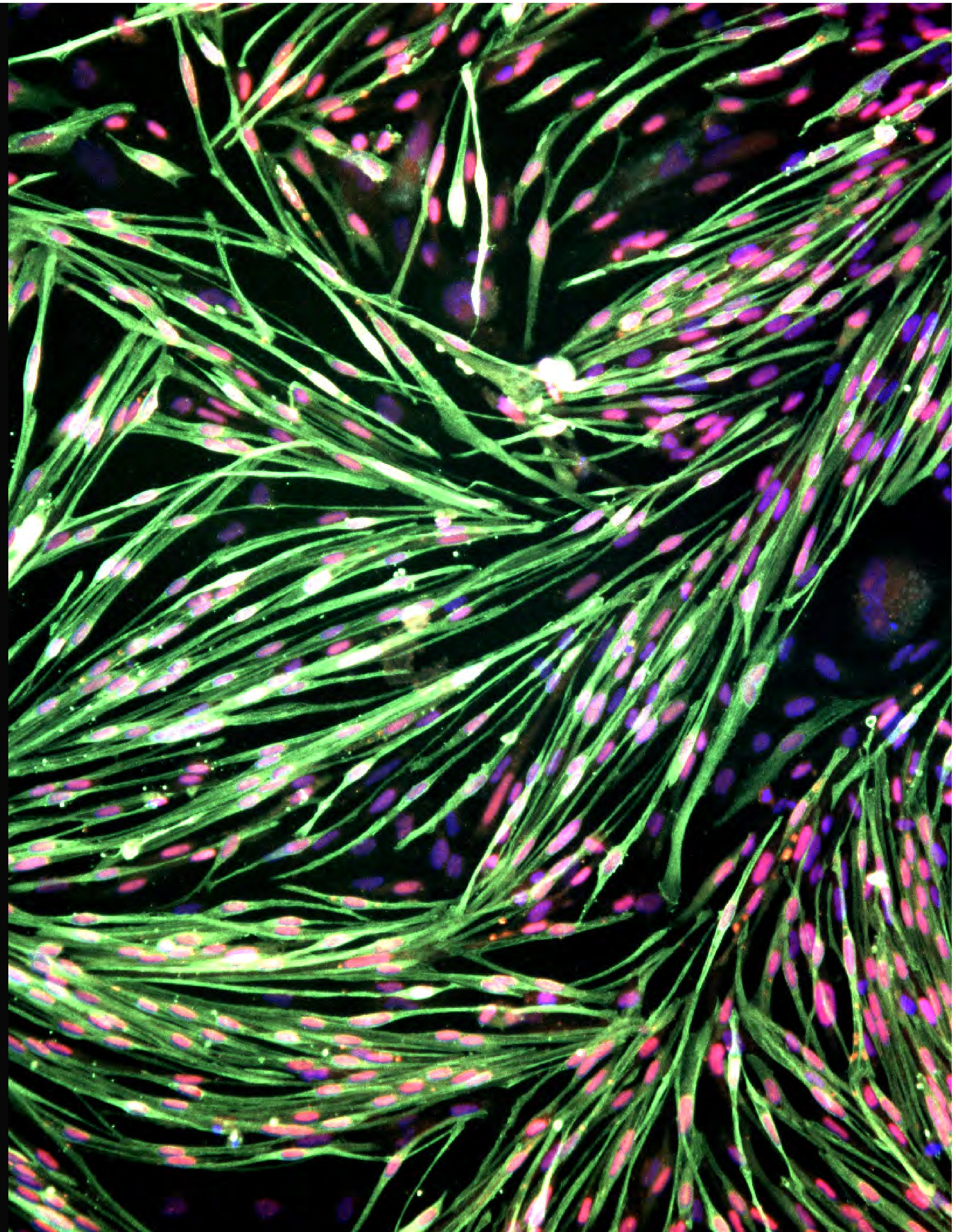
Tough Tech Summit 02.
October 24 & 25, 2019

As with our first publication, the following sections tell stories from the front lines of some of today’s most dynamic Tough Tech industries. In this case, they explore the worlds of NewSpace and regenerative medicine. Publication 02 concludes with a feature on the founders and companies within the The Engine Fund Portfolio.

New Lease on Life

Why regenerative medicine is finally poised to reach its potential.

By *Michael Blanding* for *The Engine*
Portraits by *Danilo Agutoli*



Human induced pluripotent stem cell-derived skeletal muscle cells. The red and and green stains are for skeletal muscle-specific proteins MYOD1 and Myosin Heavy Chain, respectively, and the nuclei are stained blue with DAPI. *Image courtesy of:* Cellino

Twenty-seven years ago, Doug Melton's son Sam woke up sick and throwing up, and he and his wife rushed their six-month-old baby to the hospital. A doctor gave them a sober diagnosis: Sam had Type 1 diabetes, meaning his body was attacking the beta cells in his pancreas that produced insulin. Without regular injections, he wouldn't survive. The pronouncement sent the family into turmoil. "You have a six-month-old son, and they can't tell you, stop coming to me in the middle of the night and pricking me with that needle," says Melton, then a Harvard biologist researching frog development. "They have to watch what they eat, measure their blood sugars, inject themselves with insulin. At what age do you give your child the responsibility to take that on, knowing that if they don't, they will die?"

The next year, Melton completely changed his research practice to focus on finding a cure for the disease, a project that became more urgent when his daughter Emma also received a diagnosis at age 14. Now Co-Director of the Harvard Stem Cell Institute, Melton has placed his hopes on a bold proposition: using stem cells to regenerate the beta cells within the body to produce more insulin. Down the hall from Melton's office, lab technicians inside a beta-cell "foundry" take stem cells—cells which have not yet differentiated into a specific tissue type—and subject them to a complex recipe of small molecules and growth factors. After some 15 different steps over six weeks, the solution resembles pink strawberry soda containing tiny snow-globe flakes, each cluster holding some 6,000 cells.

In 2015, Melton's lab reported a breakthrough: the creation of the first functional beta cells, when injected into diabetic mice, allowed them to produce insulin for six months, demonstrating that a cure for the disease might be possible. "Now the question is, can we figure out how to put it into humans?" Melton says. He created a company, Semma Therapeutics (named after this children Sam and Emma) to test that question, raising over $150 million in funding, with hopes to go into clinical trials within the next two years. The potential market for such a therapy is enormous. Currently, up to 40 million people worldwide suffer from Type-1 diabetes, spending some $17 billion a year on insulin injections. In order to achieve success, however, Melton's company will have to not only produce viable human beta cells, but also ensure they produce the right amount of insulin in the body, and protect the cells from being rejected by the patient they are trying to help.

Beta cells aren't the only stem cell therapies that are currently showing promise. Other researchers—many in the Cambridge and Boston area—are using gene editing and other advanced techniques to turn stem cells into heart muscle and neurons that could regenerate damaged cells in the body. They have already used stem cells to effectively cure some rare diseases of the blood. Such regenerative therapies could produce new transplantable organs and even cure diseases incurable today. "I honestly believe this is achievable within our lifetime," says Melton. "It's not going to happen in a couple of years, but if we can combine genetic modification with the ability to make cells, it could change the practice of medicine."

The Magic of Stem Cells

Stem cells have long been seen as a medicinal cure-all, unlocking the potential of the human body to heal itself. "In a way it's the ultimate pharmaceutical," says Bob Nelsen, Managing Director at ARCH Venture Partners, which has funded Semma and co-founded stem cell company Fate Therapeutics. "You can treat disease, or prevent disease, or reverse aging through the cells." Despite the promise of so-called regenerative medicine, however, the reality has yet to live up to the hype. Beset by the controversy over embryonic stem cells, research into treatments lagged throughout the 1990s. Artificial organs created using stem cells simply fell apart. Biologists struggled to find ways to protect stem cells from being attacked by the hosts they were trying to heal, while timelines optimistically predicted a few years stretched into ten or more.

Recently, however, scientists and entrepreneurs have seen new hope for the field, as techniques have emerged to create stem cells without embryos. Since 2013, scientists have expedited cell transformation using gene editing technology CRISPR/Cas9, a technique to identify and replace specific snippets of DNA using guide-RNA, which functions like little zip codes to find the right place in the DNA strand to precisely change the genome. Along with that technology, new high-throughput screening techniques have allowed biologists to rapidly test multiple molecular compounds to transform stem cells. "We constantly try to gaze into a crystal ball and understand what is going to be the next frontier in medicine," says Jerel Davis, Managing Director of Versant Ventures, which helped found the company BlueRock Therapeutics. "A few years ago, we put regenerative medicine on our list as an inevitability, something that is going to fundamentally revolutionize how we develop therapeutics."

In addition to the work in producing new cell therapies, Davis says, companies are developing new ways to mass-manufacture them, and regulators are becoming more open to approving them, putting science potentially on the cusp of a golden age of regenerative medicine. "Every cell type in the human body is a new platform for new therapeutics," he says. While scientists have been making huge strides in creating new stem cells in petri dishes, however, the challenge now is to figure out how to get them into human bodies where they heal patients. "The part that hasn't happened yet," says Nelsen, "is to really understand how to deliver and target all of these cells *in vivo*."

Despite the novelty of today's stem cell therapies, scientists have known about the role of stem cells in animal embryo development for over 100 years. By the 1950s, biologists had begun exploring the role of two types of stem cells in human bone marrow: hematopoietic stem cells (HSCs), which create new blood cells; and mesenchymal stem cells (MSCs), which grow new fat, bone, and cartilage cells.

The first bone marrow transplant to treat patients suffering from blood cancers such as leukemia began in the late 1950s. For many years afterwards, however, bone marrow transplants have remained a treatment of last resort, since it requires killing patients' existing immune system with intensive chemotherapy or radiation before transplanting new stem cells that can create healthy cells. Survival rates were only 60 percent when they first started, rising to 85 percent today, and even those who survive can experience complications including stunted development and infertility. "We brought people to the edge of death," says David Scadden, Co-Director of the Harvard

> *"It's not going to happen in a couple of years, but if we can combine genetic modification with the ability to make cells, it could change the practice of medicine."*

Doug Melton
Co-Director,
Harvard Stem Cell Institute

Bob Nelsen,
Managing Director,
ARCH Venture Partners

Jerel Davis
Managing Director,
Versant Ventures

David Scadden
Co-Director,
Harvard Stem Cell Institute

Stem Cell Institute, whose office is one floor down from Melton's. "It was almost at the bounds of what was ethical. But when it worked it was miraculous."

Like Melton, Scadden was motivated to study stem cells through a personal connection: the pain his mother underwent struggling with leukemia. He currently spends much of his time in the lab focused on creating safer and better techniques for bone marrow transplants to treat cancer. Scadden is focusing on the HSC "niche," the unique chemical environment within the bone marrow that allows stem cells to thrive. Based on the analysis of high-throughput chemical and genetic screens, his lab is trying to recreate that environment in a dish in order to make more stem cells that function better. "For a long time it was a debate in the field whether cells had their own internal logic and followed their own program," Scadden says. "But that's not true. We were able to show that they don't govern themselves; they listen to the signals around them. If a neighborhood goes bad, it can corrupt a cell."

Scadden is now examining ways to treat cancer cells—not by killing them, but by treating them as stem cells that have been stuck in their development. If doctors can "change the neighborhood" with drugs to alter the chemical makeup of a cell's niche, "maybe treating cancer isn't about pounding it into oblivion with a hammer," he says, "but by releasing the brake that has caused it to be stuck. Maybe a cancer cell is not a rogue cell, but a cell that has some normal features, but has been corrupted in its differentiation program in a way that has caused it to grow in an unregulated way." By exposing them to the right environment of chemicals, maybe—just maybe—they can be reformed to become healthy contributors to the body. Through a company he co-founded named Magenta Therapeutics, he has been working to develop medicines.

Cellular Transformations

Other regenerative therapies have focused not on injecting stem cells into the body, but on transforming stem cells into other cell types to repair damaged cells within the body. In 1974, Rudolph Jaenisch and Beatrice Mintz succeeded in using a retrovirus to substitute a sequence of DNA in the nuclei of mouse stem cells in order to permanently alter their genome. This first "knock-in" mouse opened up new possibilities for stem cell therapy to overcome one of its primary challenges: the fact that new cells inserted into the body could be rejected by the immune system, leading to a serious complication known as graft-versus-host disease (GVHD). If stem cells could be created from a patient's own DNA or cells, then the body would theoretically accept the cell as its own.

> ***If stem cells could be created from a patient's own DNA or cells, then the body would theoretically accept the cell as its own.***

John Gurdon of the University of Cambridge in the UK had been able to show that DNA transfer into stem cells was possible decades earlier, by inserting the DNA into an embryonic stem cell, which successfully developed into a clone of an adult frog. By the 1998, scientists had isolated embryonic stem cells (ESCs) in humans. At the time, however, controversy over the use of human embryonic stem cells threatened to halt regenerative medicine research, and Jaenisch and others began searching for a new way to create stem cells that would not involve using human embryos. Gurdon's experiments had shown that any cell in the body had within it all of the genetic material necessary to create any other cell.

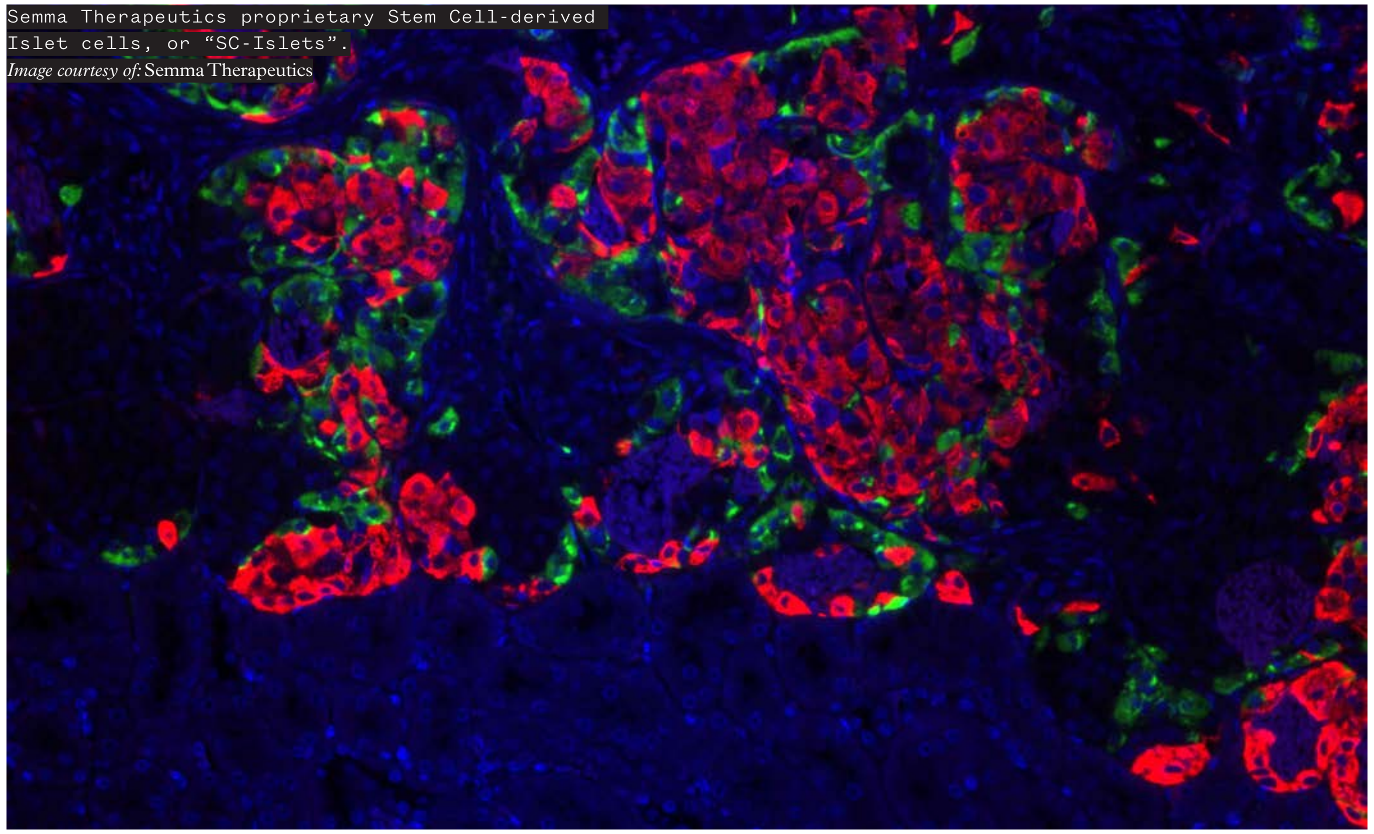
Enter Shinya Yamanaka and Kazutoshi Takahashi in the early 2000s. As researchers at Kyoto University in Japan, they identified just four active genes that could together make any cell pluripotent, essentially creating the equivalent of an embryonic stem cell from an adult cell. They created the first induced pluripotent stem cells (iPSCs) from both mice and humans in 2006. (Gurdon and Yamanaka shared the Nobel Prize for these discoveries in 2012.) That invention just over a decade ago opened the floodgates in regenerative medicine, showing that scientists could create stem cells from a patient's own blood or skin cells, without any embryos at all.

Jaensich, now at MIT's Whitehead Institute, was the first to use iPSCs therapeutically in animals in 2007 when, along with Tim Townes of the University of Alabama at Birmingham, he was able to take cells from the tail of a mouse suffering from sickle-cell anemia, and induce them to become stem cells. The researchers then differentiated the cells into healthy HSCs without the sickle-cell mutation, and inserted them into the mouse's bone marrow, creating new healthy red blood cells.

Researchers are now using all of these kinds of stem cells—HSCs, MSCs, ESCs, and iPSCs—to develop medicines for treating diseases in humans. Donald Kohn of UCLA, for example, has genetically modified patients' own HSCs to treat adenosine deaminase-deficient severe combined immunodeficiency (ADA-SCID), also known as bubble-baby disease due to its severe inhibition of the immune system that can make a common cold fatal. Last year, he announced that nine out of ten children in clinical trials were cured from the disease.

Other clinical trials are currently underway to use patients' own genetically modified HSCs to treat other blood disorders such as sickle-cell anemia and beta thalassemia in the same way—removing patients' stem cells, genetically modifying them, and then returning them to the body where they will hopefully produce healthy red blood cells. Currently, three companies—Intellia Therapeutics, CRISPR Therapeutics, and Editas Medicine—are using CRISPR technology to edit the DNA in HSCs to attack diseases. The Switzerland- and Cambridge-based CRISPR Therapeutics began enrolling patients in a new clinical trial in October to remove HSCs of patients with sickle-cell anemia, genetically modify them to correct the mutation that prevents them from holding enough

Marinna Madrid, Co-Founder, Cellino & Nabiha Sakyalen, Co-Founder & CEO, Cellino
photo by Doug Levy.



Semma Therapeutics proprietary Stem Cell-derived Islet cells, or "SC-Islets".
Image courtesy of: Semma Therapeutics

hemoglobin, and then insert them back into patients. It hopes to begin another trial targeting beta thalassemia in Europe by year's end.

While CRISPR technology has advanced in editing genetic material, it can still be a challenge to get the guide-RNA into cells in order to make the necessary substitutions. Traditional genetic engineering using viruses is expensive and can potentially introduce unintended (and unwanted) genomic changes into cells; lipofection, which uses fat molecules to penetrate cell membranes, only works with certain cells, and nanoparticles can leave metal and polymer residues behind. To address that problem, Cambridge-based startup Cellino has developed a novel technique using laser pulses to get genetic material into cells. "It allows you to precisely manage the delivery of these zip codes into the cell at the right time in the right order," says CEO Nabiha Saklayen.

The company grew out of Harvard's School of Engineering and the Wyss Institute, and is now financed and based at The Engine, built by MIT. Cellino's technique uses a nanopattern surface studded with tiny pyramids covered in a metal coating. iPSC cells are cultured directly onto the surface, and a laser is pulsed across the surface. As the laser energy is absorbed, it creates a nanobubble that temporarily opens a hole in the cell, allowing guide-RNA floating in solution to enter the cells. Within 20 to 30 seconds, the cell membrane closes with the material inside.

The technology can speed creation of cells over other techniques, Saklayen says. "One cell type that takes over 90 days in a dish, we've been able to create in three days," she says. "It opens up a world of possibilities." According to Chief Science Officer Stan Wang, formerly of Harvard Medical School, the company is planning to use a high-throughput system to rapidly experiment with engineering different cell types relevant to treating human disease as early as next year.

Beginning With the Blood

It's no accident that the first stem-cell therapies involve diseases of the blood. Having single cells in a liquid medium makes it easier to take cells in and out of the body and still have them function. New research, however, has begun to concentrate on regenerating other types of cells and tissues. Cambridge-based BlueRock Therapeutics—funded by $225 million partnership between Versant and pharma giant Bayer AG—has focused on cells derived from ESCs and iPSCs, including dopaminergic cells to treat Parkinson's disease and cardiomyocytes to repair muscle cells in the heart. "We wanted to create an off-the-shelf solution by identifying cell populations where we know what the deficiency is," says Versant's Davis. "In Parkinson's, for example, we know you lose dopaminergic neurons and that leads to the symptoms, so BlueRock's approach is to replace that exact cell type."

To do that, the company plans to use a combination of transcription factors, proteins, and small molecules, in order to push the iPSCs down the path to becoming a specific cell type without directly editing their DNA. For dopaminergic cells, for example, it will use a protocol developed by Lorenz Studer, Director of The Center for Stem Biology at Sloan-Kettering Memorial in New York and scientific co-founder of the company. The process uses a combination of three molecules to trigger something called the "wingless-type MMTV integration site (WNT) signaling pathway" to turn iSPCs into functioning nerve cells. These cells will then be implanted into the brain in an attempt to restore lost motor function.

For heart cells, the company plans on subjecting cells to a similar process in order to repair damaged tissue after a heart attack. For that process, the company is working with Michael Laflamme and Gordon Keller of the University of Toronto, who have managed to direct iPSC cells down the pathway into heart muscle cells. They are currently working on increasing the maturity of the cells in order to reduce their likelihood of arrhythmia (irregular heartbeat) before they are ready to implant into humans. BlueRock plans to enter clinical trials on the dopaminergic cells by year's end, with cardiomyocytes to follow.

One company that is already involved in human clinical trials is ViaCyte, which, like Melton's Semma Therapeutics, is pursuing a stem cell–based therapy to tackle Type-1 diabetes. The company has used small molecules to drive embryonic stem cells into something called pancreatic precursor cells, in the hopes that once implanted into the body, the cells will continue to evolve into endocrine cells that will produce insulin. "They are not functional at the time of transplantation, but they become so after development *in vivo*," says ViaCyte's Chief Science Officer Kevin D'Amour. Unlike in most diseases, in which researchers have to worry about the body rejecting implanted cells, the entire nature of Type-1 diabetes is that the body attacks its own beta cells, whether they come from another donor or not.

Because of that, ViaCyte has had to work to create a capsule in which to hold the implanted cells that will separate them from the body's immune cells that seek to destroy it. Researchers often liken it to a "tea bag," a semi-permeable membrane that can hold the cells and allow them to infuse the body without directly coming into contact with the blood. After implanting them in patients starting in 2015, however, researchers found that the body walled off the capsule with a layer of skin cells. "We saw a pretty aggressive response," says ViaCyte CEO Paul Laikind. "The body is really trying to isolate that foreign body." The company has suspended that trial while it works with W.L. Gore, the makers of Gore-Tex, to design a fabric for resisting the foreign-body response.

In the meantime, it started pursuing another clinical trial last year with a differently designed capsule that will allow blood vessels to penetrate the capsule and come into direct contact with the beta cells. While that should obviate the difficulties with rejection of the capsule, it will also require immunosuppression therapy to prevent the body from attacking the cells themselves. Even so, ViaCyte is hopeful that it can achieve therapeutic levels of insulin in the near term. "We hope it will be possible to demonstrate efficacy in six to twelve months," says Laikind. Not taking anything for granted, the company has also partnered with gene-editing company CRISPR Therapeutics in order to try and genetically modify its precursor cells in order to protect them from the body's immune response.

New Discoveries

While developments in stem cell biology from HSCs to embryonic stem cells to iPSCs has opened up new possibilities in regenerative medicine, one of the most exciting developments is the discovery that the body has multiple types of stem cells specific to organs, which may have the capacity to self-heal, if scientists can figure out how to switch them on. These so-called endogenous stem cells have been found, so far, in the liver, lungs, and intestine, and possibly the heart, and hold promise for regenerating their corresponding organs both inside and outside the body.

In 2009, Cedar-Sinai's Eduardo Marban reported the results of the first clinical trial involving such endogenous stem cells, taking cells derived from the hearts of heart-attack patients, culturing them, and infusing them back into the body. The results, published in *The Lancet* in 2012, showed regeneration of healthy heart muscle, the first successful

Endogenous stem cells have been found, so far, in the liver, lungs, and intestine, and possibly the heart, and hold promise for regenerating their corresponding organs both inside and outside the body.

Stan Wang
Co-Founder & CSO, Cellino

Kevin D'Amour
CSO, ViaCyte

Paul Laikind
CEO, ViaCyte

Derrick Rossi
Co-Founder of Intellia Therapeutics and Magenta Therapeutics

> ***If scientists do succeed in creating organs artificially, however, it could dramatically improve the chances of survival for those needing organ transplants due to disease or injury.***

therapy of its kind. Despite such promise, however, patients did not see significant improvement in heart function, and later studies by Marban and others have shown mixed results.

A new direction in stem cell therapy is in treating endogenous stem cells while they are still inside the body, rather than removing them and re-inserting them. "The premise is that endogenous stem cells already exist inside the body, if we can only stimulate them to do what they would normally do," says Derrick Rossi, a researcher at Children's Hospital in Boston and co-founder of Intellia Therapeutics and Magenta Therapeutics. He recently became President and CEO of a new company, Cleveland-based Convelo Therapeutics, which is attempting to use endogenous stem cells in the central nervous system to treat multiple sclerosis. That disease is caused by destruction of the myelin sheath that wraps and insulates nerves inside the body, leading to a devastating range of symptoms from impaired vision to loss of muscle function.

Convelo is based on science by Case Western Reserve's Paul Tesar and Drew Adams who discovered something called oligodendrocyte progenitor cells (OPCs) within the central nervous system, which could grow into cells responsible for re-myelination of nerves. They found that by targeting these OPCs with a combination of small molecules, they could block specific enzymes that inhibit their growth, and trigger them to regenerate myelin. With funding of $7.8 million from private donors, the company is now moving to test the drugs inside the body.

Tesar and Adams have not only used stem cells in their nerve cell therapy, but they have also used stem cells in the laboratory to construct human brain tissue on which to test their theories, rather than using mice or rats. Researchers have been using such "organoids" since 2008, when Yoshiki Sasai, a biologist at the Japanese research institute RIKEN, showed that embryonic stem cells could be coaxed into a dish to self-assemble into 3-dimensional tissue structures. Since then, scientists have produced organoids from both iPSCs and endogenous stem cells, creating virtual hearts, lungs, brains, kidneys, livers, and intestines. The development could reduce the cost and ethical concerns of using animals for research, as well as allowing researchers to experiment directly with human tissue, which might produce more accurate results earlier than using mice, rats, or monkeys. Scientists could even create patient-specific organoids that could allow them to personalize testing of potential treatments.

Growing tissues from such tiny organoids into full-fledged organs that might one day be transferred into the human body to replace a damaged or faulty organ, however, has proved a much more challenging endeavor. Back in the 1990s, Joseph Vacanti of Massachusetts General Hospital and Robert Langer of MIT pioneered a technique for building organs using biodegradable polymer scaffolding, seeded with stem cells. Build it, they thought, and the cells would do the rest, populating the scaffolding and performing the functions for which they were designed. While the process gave scientists key insights into how cells operate, it has ultimately been a failure.

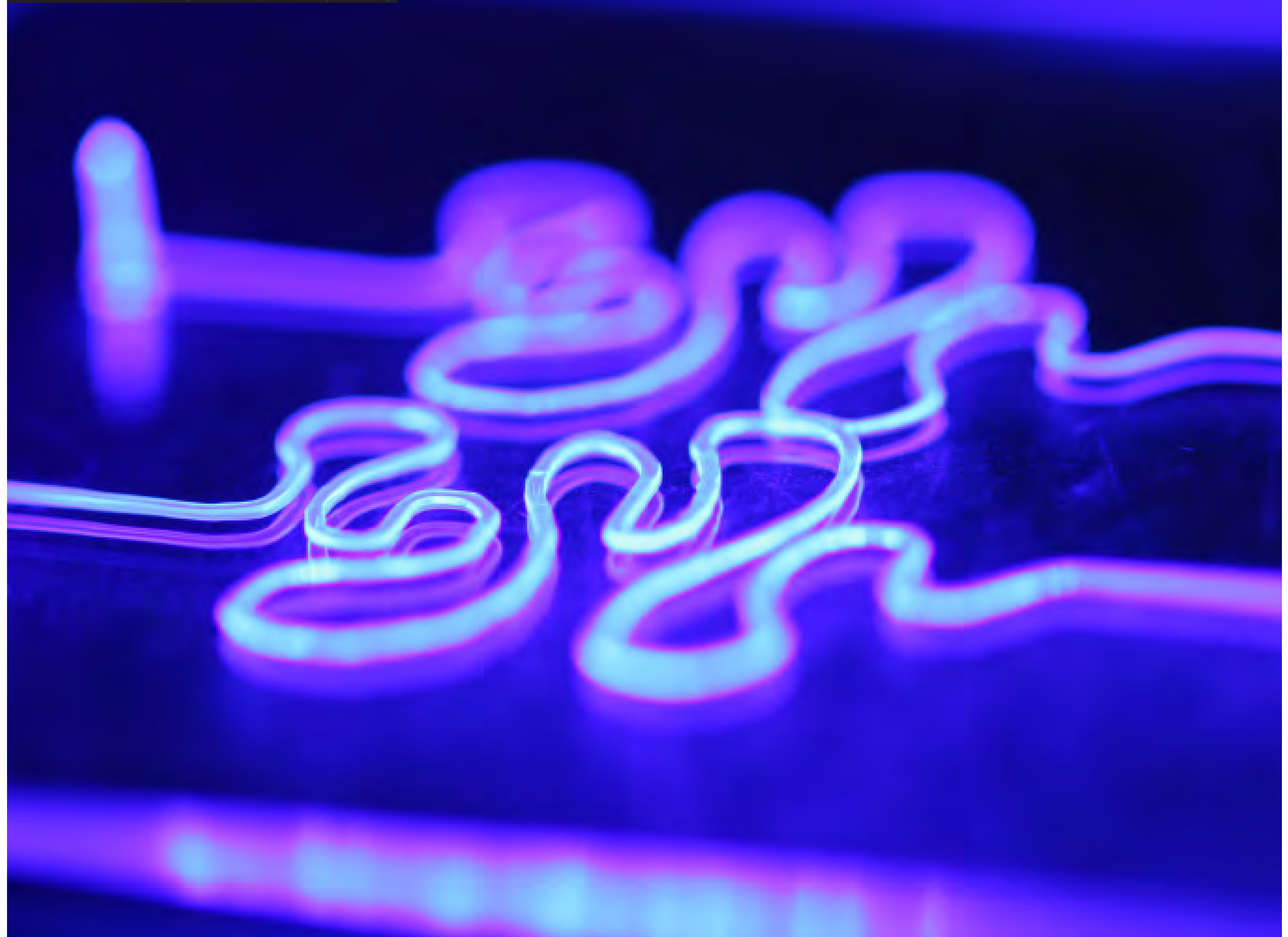
Thus far, there have been few successful transplants of an artificial organ created through synthetic scaffold. In 2006, Anthony Atala of Wake Forest School of Medicine was able to grow artificial bladders and successfully transplant them into patients. He has since also used the techniques to construct artificial vaginas. In 2011, surgeon Paolo Macchiarini at the Karolinska University implanted an artificial trachea into a cancer patient. Macchiarini repeated the procedure with a half-dozen other patients; however, nearly all of them died, and the university suspended its efforts after an inquiry questioning Macchiarini's methods that found him guilty of ethical breaches in the way he represented the treatment.

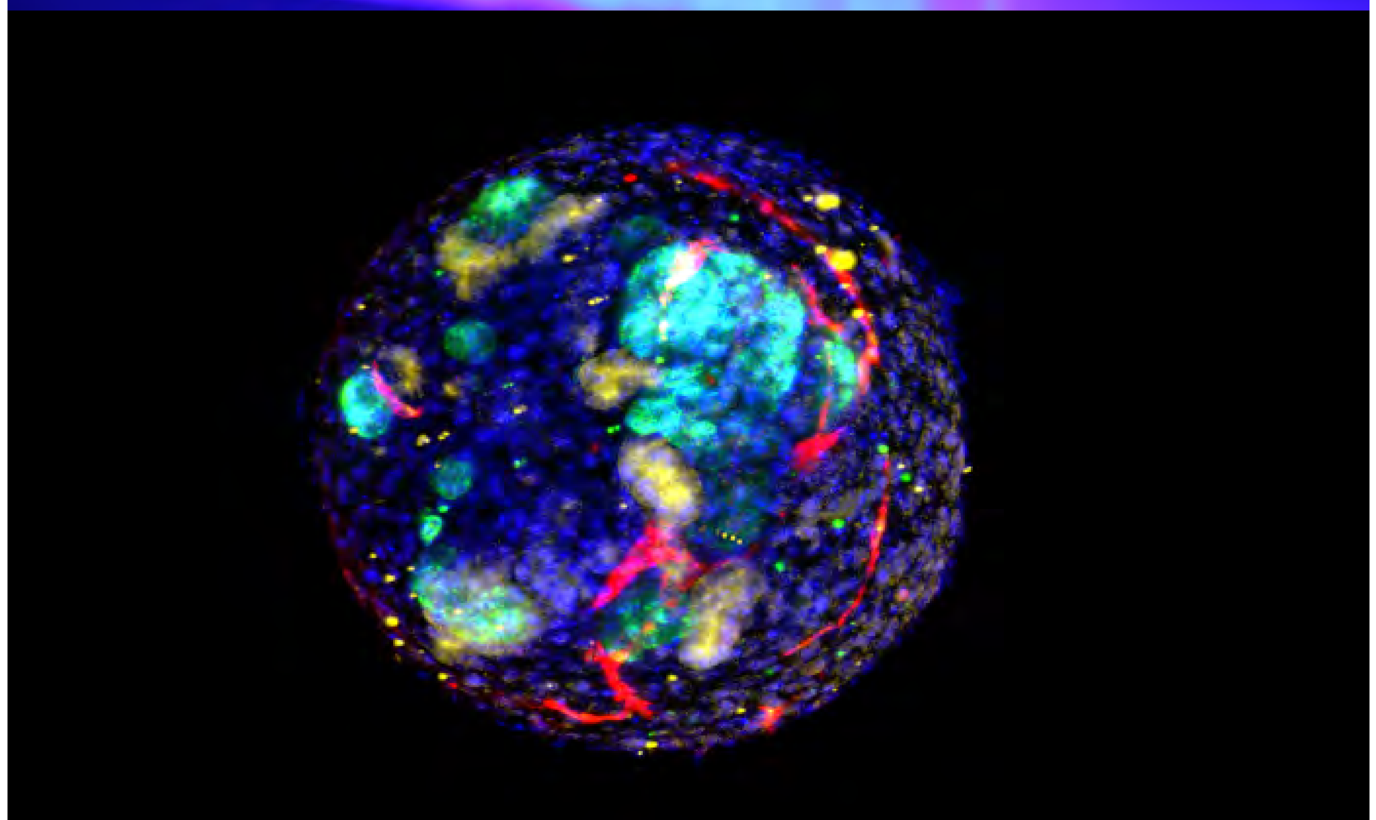
All of these organs, however, are relatively simple in both structure and function. For more complex organs, no polymer scaffold was developed in the 1990s and early 2000s that was able to replicate their fine-tuned structure, especially the vasculature of millions of blood vessels needed to keep them healthy and alive. "At the time, there was no good scaffolding that could generate a human-scale organ," says Harald Ott, a heart surgeon and organ engineer at Mass General. "The heart is not just a blob." Attempts to regrow heart muscle by infusing stem cells into patients, however, also seemed not to be working. "It would have been great if it did," Ott says, "but it's not necessarily surprising that it wasn't a magic bullet."

Growing Organs

Starting in 2005, Ott began pursuing a novel approach to creating a new scaffold by using donor organs, but stripping them of their original cells that might be rejected by a new host, while leaving the extracellular matrix intact. Then, theoretically, that scaffold could be repopulated with a patient's own cells. Ott tried many different techniques and chemicals in an attempt to purge organs of their cells. "Up until the day it worked, everyone in the lab said, we can put you on our paper if yours doesn't work out. It was a crazy high-risk project." Finally, Ott hit paydirt

Fugitive ink printed in the shape of a convoluted proximal tubule in the kidney.
Image courtesy of: Kimberly Homan, Jessica Herrmann, David Kolesky, and Jennifer Lewis from Harvard University and the Wyss Institute for Biologically Inspired Engineering.





Confocal light microscopy 3D rendering of a kidney organoid derived from stem cells (all cell nuclei in blue, glomerular-like cells in green, proximal tubule-like cells in yellow, vasculature in red).
Image courtesy of: Kimberly Homan, Katharina Kroll, and Jennifer Lewis from Harvard University and Navin Gupta and Ryuji Morizane from Brigham and Women's Hospital.

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Harald Ott
Heart Surgeon & Organ Engineer,
Mass General Hospital

Martin Yarmush
Funding Director of The Center
for Engineering in Medicine,
Mass General Hospital

Mehmet Toner
Center for Engineering in Medicine,
Mass General Hospital

George Church
Founding Core Faculty Synthetic
Biology, Wyss Institute at Harvard
University

with a combination of detergents including sodium-dodecyl sulfate (SDS), which caused cells to lyse, or break open, while keeping the extracellular matrix and its sturdy protein core intact.

The next problem was to put new cells onto that matrix. Ott started with a rat heart matrix, seeding it with fetal cardiomyocyte cells, which are already partially differentiated into heart muscle cells. After only eight days of maturation, the cells had grown enough so that they could be stimulated with an electrical pulse to produce a heartbeat. Ott's lab has since used similar techniques using iPSCs to create hearts, kidneys, liver, and pancreases for rats and pigs, and has begun working on human organs. Recently, he created a rat intestine seeded with human stem cells that was able to absorb nutrients for four weeks, and a rat-sized pancreas that was able to cure diabetes for weeks. Despite those successes, he is realistic about how complicated a road he still has to travel. "It's still very high-risk research," says Ott, "It's hard for me to get the financial support to perform this kind of academic research and development, and find the researchers who are willing to make this high-risk decision for their career."

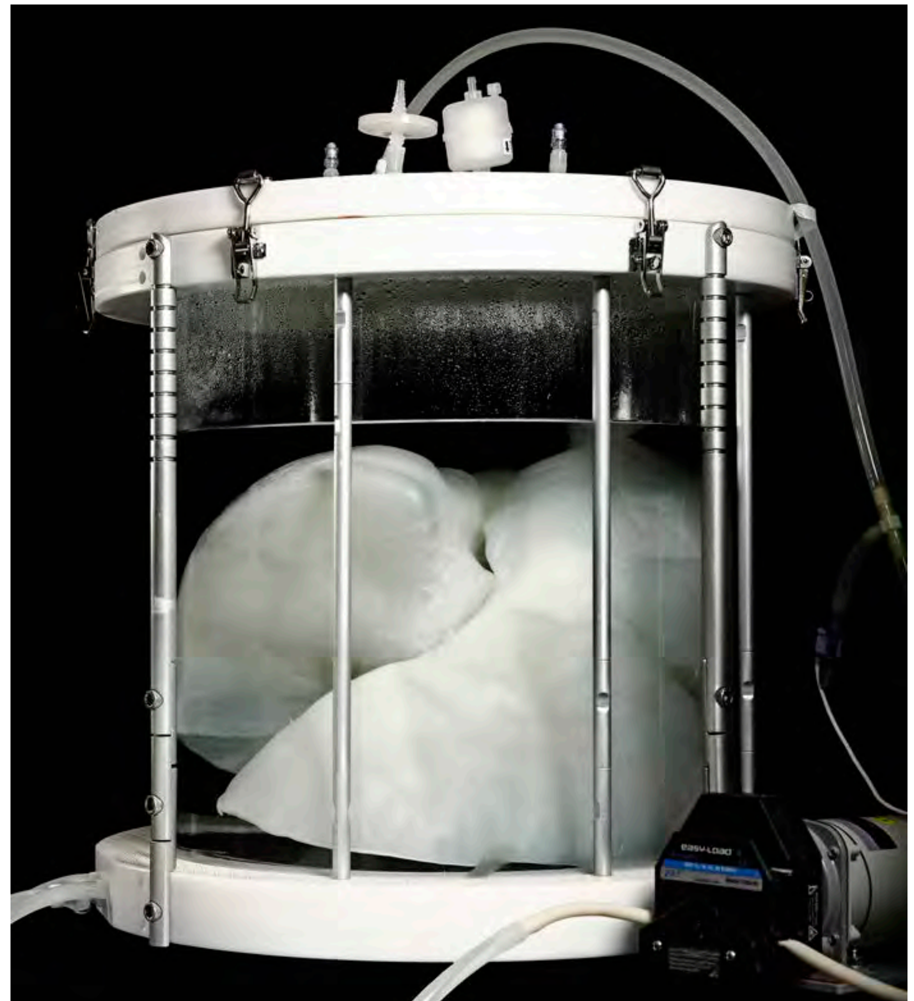
Combined with techniques to create artificial organs, preservation technology like Toner's could bring us closer to a day when organs are available "off-the-shelf" for patients, ready to be used at a moment's notice—whether they are generated from their own cells or created from iPSCs.

If scientists do succeed in creating organs artificially, however, it could dramatically improve the chances of survival for those needing organ transplants due to disease or injury. According to government statistics, last year some 35,000 organ transplants were performed in the U.S.; however more than 100,000 people are currently on the waiting list for an organ. Each day, 20 people die waiting for a transplant. Ott's colleague at Mass General, Martin Yarmush, is working on ways to extend the lives of organs removed from the body so that more organs can survive to be transplanted. "There are millions of cadavers, from motorcycle accidents and such, that are perfect specimens of human beings, but after 30 minutes, an organ will lose all of its function," says Yarmush, the Founding Director of the Center for Engineering in Medicine.

His lab has been working on techniques to perfuse organs that have been deprived of oxygen and nutrients, so they can be transplanted. So far, he has been able to take a rat liver that has been 60 minutes outside of the body at room temperature. "You put it into a perfusion device and perfuse it with media and other goodies, and you can get nearly 100 percent transplantation rate. If you leave it out for 60 minutes without putting it in a restore solution, you get zero."

Another colleague at Mass General, Mehmet Toner, is working on ways to extend the life of organs for even longer periods of time. Even if an organ is kept cool, he says, it can't be stored for more than a day outside the body. Freezing an organ down to cryogenic temperatures, however, damages vital tissue function. Toner's lab is working on ways to preserve organs by cooling them down to intermediate temperatures, cool enough to slow metabolism long enough to preserve them for weeks or months without damaging them. Currently, he's been able to preserve a rat liver for a week before transplanting with no harmful effects. It's important to note that alternative organ preservation techniques using warm, flowing, nutrient-rich blood, like the Transmedics Organ Care System, represent a fundamental step forward from traditional cold ischemic storage, but do not address the longer preservation timelines being investigated by Toner's lab.

Combined with techniques to create artificial organs, preservation technology like Toner's could bring us closer to a day when organs are available "off-the-shelf" for patients, ready to be used at a moment's notice—whether they are generated from their own cells or created from iPSCs. "When you need an aspirin, you don't call someone who makes it for you, you go to CVS," says Toner. "For cell therapies to become easily usable, you need to be able to stabilize them so they can be used when needed."



A pair of decellularized pig lungs in a bioreactor.
Image courtesy of: The Ott Lab / Massachusetts General Hospital

Pig Hearts and Organ Printing

A more radical method to ensure we have viable organs available when we need them is being developed by George Church, a geneticist at Harvard Medical School and Harvard's Wyss Institute for Biologically Inspired Engineering who helped invent CRISPR. Among other projects, he and former graduate student Luhan Yang are working to develop organs in pigs for transplanting into humans, a method known as xenotransplantation. Previously, he says, scientists have explored the idea of using pig organs as scaffolds, decellularizing them and replacing them with human stem cells. To Church and Yang, however, that just requires an extra step. "You are going to sacrifice the animal anyway. With the option we are pursuing, one animal can produce dozens of useable components for transplantation, and you can synchronize it before and after so they are ready when you need them," he says.

Using pig organs poses its own challenges, however. One large concern is the presence of porcine endogenous retroviruses (PERVs) that could infect human cells and cause disease; the other worry is that the human body might reject the organ outright as a foreign object. Church and Yang formed a company, eGenesis, to tackle these issues. In 2015, they succeeded in using CRISPR to knock out the PERV genes in more than 60 different places in the genome of a pig; now, they are in the process of breeding a strain of PERV-free pigs in China. "We don't have to do any fancy molecular biology; we can just breed them like pigs," Church says. Now, the company is working on a separate project using CRISPR to knock out pig genes that provoke a response in the human immune system. "You trick the human immune system into believing that otherwise incompatible cells are okay," Church says. Eventually, the hope is that they can breed the two strains of pigs together to produce pigs safe enough to donate their organs to humans in a virtually endless supply.

Both recellularization and xenotransplantation require some harvesting of organs in order to transplant them into a new body. A third method for organ engineering, however, aims to literally produce them from scratch. Church's colleague at the Wyss Institute, Jennifer Lewis, has produced a 3D bioprinter that she is using to artificially print organs that could later be transplanted into humans. The idea grew out of earlier techniques to produce synthetic organs from polymers that could replicate human organs. In the midst of trying to create synthetic analogues for tissues and vascularization, however, Lewis and her colleagues decided to just create organs for real. "We said, we don't have to emulate biology. We can *do* biology," she says.

Her technique consists of three different types of "inks"—a sacrificial ink that can help template vascular networks; a biopolymer ink to create a extracellular matrix for the organ scaffold; and finally, a cell-laden ink containing mesenchymal stem cells, iSPCs, or organoids to replicate the living cells of the organ. The machine would then coordinate all three of these inks to print the organ. "The challenge, of course, is to replicate the architectural complexity and cellular density of the organ," Lewis says. "If you do all of that, then hopefully that means you have something that not only looks like an organ, but also functions like one."

Her next step is to print tissue that could be used in animals. "We are very much in the infancy in this process," she admits, "but we certainly hope our work is providing some foundational basis for many labs around the world."

Short of creating working organs

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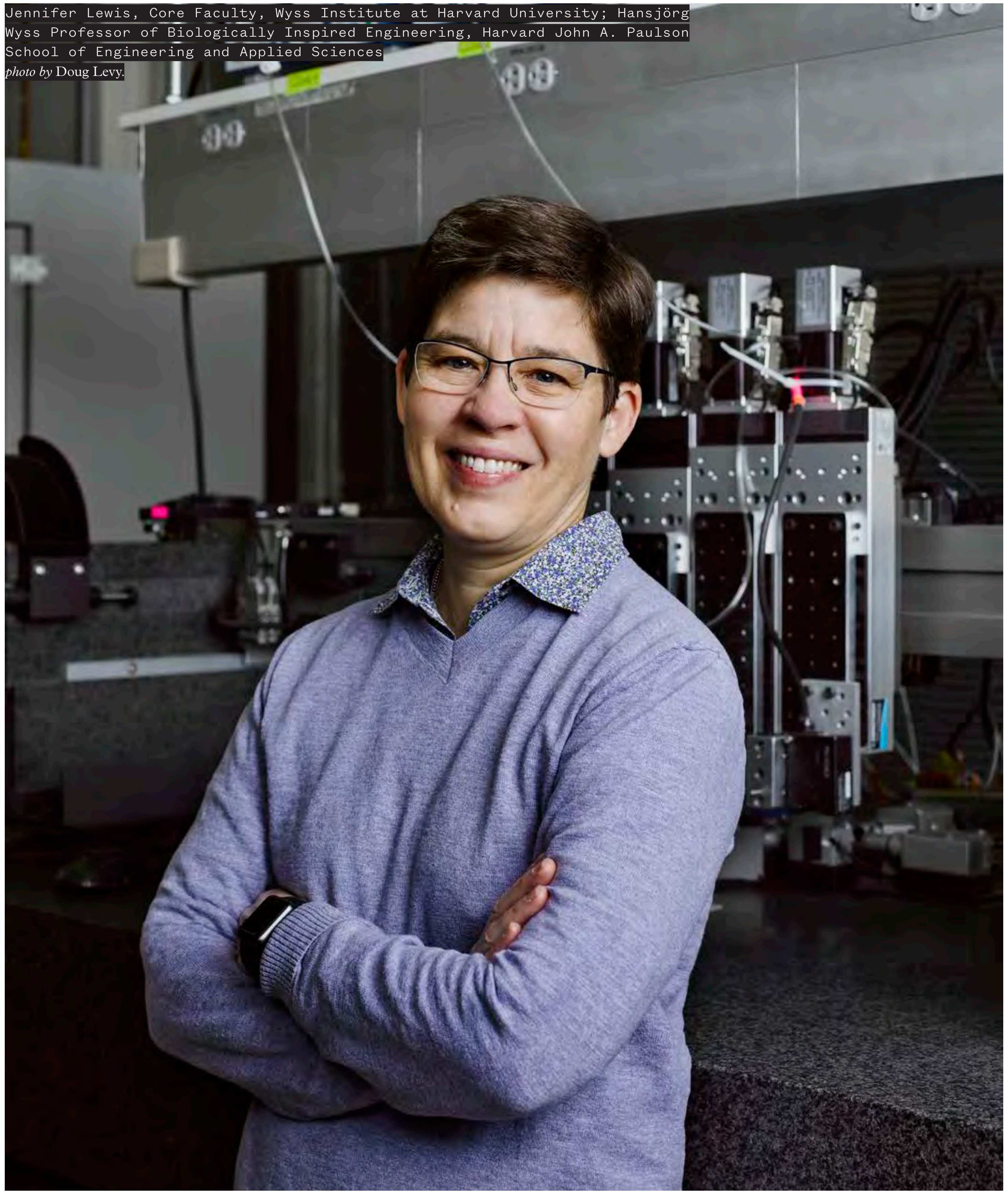


Jennifer Lewis, Core Faculty, Wyss Institute at Harvard University; Hansjörg Wyss Professor of Biologically Inspired Engineering, Harvard John A. Paulson School of Engineering and Applied Sciences
photo by Doug Levy.

for transplantation, 3D bioprinting can also produce artificial organ structures for medical research. So-called "organs-on-a- chip" are like organoids in that they can consist of actual human tissue *in vitro* to test drugs and toxins as an alternative to animal testing. Using mechanical and electronic engineering, however, they can also be stimulated to recreate organ function as well. "We can mimic physiological breathing in the lungs, peristaltic-like motions in the intestine, and pulses in the heart," says Don Ingber, the Wyss Institute's Founding Director.

Ingber first participated in the creation of a lung-on-a-chip, recreating alveoli sac and alveolic-capillary interface on a metal chip covered in silicone rubber. "It included incredible levels of functionality," says Ingber. While traditional cell culture allows testing on a single cell type, organs-on-a-chip can include layers of different cells, printed on top of one another, to simulate the complete organ function. That, in turn, could help drug companies more accurately conduct research into new therapies. "Seventy-five percent of drugs fail in clinical trials," Ingber says. "That's because animal models don't adequately predict what will happen in humans."

The future of regenerative medicine is likely to come not from any one technique, but from a combination multiple technologies.

Don Ingber
Founding Director, Wyss Institute

Ingber is scientific founder of Emulate, a company working to create a "body-on-a-chip" that would network several artificial organs together with channels to further explore the interactions between organs. In the future, those structures could be created with a patient's own stem cells in order to test the efficacy and side effects of multiple drugs, before deciding on which to use inside the body. Outside of individualized treatment, a drug company could create an organ- or body-on-a-chip custom-designed for a certain genetic subgroup to demonstrate efficacy for a drug that might otherwise be seen as a failure in typical animal models. "That could be a game-changer for drug development," Ingber says.

The future of regenerative medicine is likely to come not from any one technique, but from a combination multiple technologies: using CRISPR to edit genes and small molecules and growth factors to drive stem cells towards certain cell lineages, as well as using stem cells to build organs inside and outside of the body in order to improve human health. "In the early days of stem-cell biology, we thought it offered the opportunity to use things like blood stem cells as replacement parts," says Scadden. While undoubtedly that is true, he says, "That's a very narrow way of looking at regenerative medicine. Now it's clear that it can also help us create models for diseases, and also give us medicine to trigger the cells inside of our body to heal itself."

That combination of therapies, in turn, could fundamentally change the way medicine is practiced and life is lived. Patients could have individual therapies developed and tested for them on artificial organs outside the body before using them inside the body. And given the strides that regenerative medicine has made within the last 50 years, its likely that within the next 50 years what once seemed like science fiction could become a reality—a near-inexhaustible supply of replacement cells and organs available to us, created from our own cells or others, to repair and replace any part of the body that fails. If regenerative medicine is able to achieve that, as seems possible, it will truly be revolutionary./

GLOSSARY

Beta cell: cells in the body that produce insulin.
Bioprinting: 3D printing technology that can produce living tissues.
CRISPR Cas9: gene-editing technology that uses an enzyme and guide RNA to replace DNA sequences. Short for "clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9."
Decellularization: removal of cells from an organ, while leaving the extracellular matrix intact.
Embryonic stem cell (ESC): cell from early-stage embryo that can develop into any cell type in the body.
Endogenous stem cell: a stem cell found within specific tissues in the body that can regenerate new cells of that tissue.
Extracellular matrix: three-dimensional network of molecules such as collagen and glycoproteins, that provides structural support for cells of an organ.
Gene editing: Technology allowing biologists to change an organism's DNA by adding, removing, or altering genetic material.
Graft versus host disease (GVHD): potentially serious complication caused by rejection of cells or organs introduced into the body.
Growth factor: molecule, such as a protein or hormone, that can stimulate cellular growth.
Hematopoietic stem cell (HSC): cell found within blood and bone marrow that can develop into any type of blood cell.
Induced pluripotent stem cell (iPSC): adult cell that is transformed into a stem cell with the capability to turn into any cell of the body.
Mesenchymal stem cells (MSCs): multipotent stem cells found in bone marrow that can differentiate into a variety of bone, muscle, and cartilage cells.
Multipotent: the ability of a cell to develop into many, but not all, different cell types.
Niche: microenvironment within tissues that can determine how stem cells differentiate.
Organoid: three-dimensional cluster of cells that can serve as simplified version of a specific organ in the lab.
Organ on a chip: combination of living cells and mechanical components that can simulate the activities and physiological response of an organ in the lab.
Pluripotent: able to differentiate into any type of cell in the body.
Polymer scaffold: artificial version of the extracellular matrix designed to be populated with living cells to create an organ in the lab.
Recellularization: process of populating cells onto extracellular matrix in order to create a functioning organ.
Small molecules: molecules of low molecular weight, such as sugars or amino acids, which can stimulate a biological process.
Xenotransplantation: process of transplanting an organ or tissue from one species into another.

The New World of NewSpace

The Technology and Companies Powering Today's Space Revolution

By *Emily Calandrelli* for *The Engine*
Illustrations by *Camilo Zuñiga*

The NewSpace industry may be built with new technology, new modes of thinking, new sources of funding, but the ethos it embodies is as old as humanity itself. It is one of daring, invention, and the pursuit of something entirely new.

From Space Race to NewSpace

On October 4, 1957, the Soviet satellite Sputnik chirped to life from the vacuum of low Earth orbit. The Space Age had begun, and with it an unprecedented period of scientific and engineering innovation. For nearly five decades following those first transmissions, the world's largest governments competed and collaborated to put progressively more complex craft into space. While orbit may have been the domain of government, getting there was very much a joint effort between public and private sectors.

The US government, for example, recruited private contractors to assist in the production of mission-specific componentry while retaining strict engineering and strategic oversight. In some ways, the private contractors vital to the US space program were so integrated, and so supervised, that they essentially served as arms of NASA itself. Such collaboration helped NASA delegate responsibilities to different congressional districts, ensuring political sustainability while accelerating technological progress far beyond the confines of the space program.

In the early 1980s and into the 1990s, the economies of collaboration were changing. NASA began to experiment with shifting more responsibility to the private sector within certain facets of the space program. The efforts failed to gain serious traction. But initiatives like SPACEHAB and the X-33 / X-34 spaceplanes, along with companies like Pioneer Rocketplane, Kistler Aerospace, and Orbital Sciences Corp. proved that the private sector had the interest, passion, and capability to reach orbit.[1]

Then, in the early 2000s, with US government programs like Alternate Access to Station (AAS) in 2000; Constellation in 2004; and, perhaps most importantly, Commercial Orbital Transportation Services (COTS) in 2006; the prospect that activities in low Earth orbit would shift to the private sector was no longer an uncertainty—it was inevitable.

Today, a new generation of private space startups has emerged without sole dependence on government funds for support. These startups are working with parties both private and public, engineering new solutions to problems both orbital and terrestrial. They have seen billions of dollars of investment and have already started to change humanity's perspective on its place in the stars.

We are living in the era of NewSpace.

Defined by its prioritization of commercially viable access to space, NewSpace is at once a movement and a philosophy. It is a product of policy shifts decades in the making as well as the rapid evolution of essential technology. The US government has relaxed its oversight and maintained vital subsidies, while private hardware and software manufacturers, bolstered by robust global competition, continue to create smaller, lighter, more powerful devices, many of which can be used off-the-shelf by NewSpace startups.

NewSpace is an increasingly complex and nuanced ecosystem of startups, technology, policy, and capital. The following aims to provide a succinct overview of the current state of NewSpace by analyzing market trends and investigating the technologies that make it all possible.

(1) Commercial Orbital Transportation Services, A New Era in Spaceflight; 2014

PAZ mission launch.
photo by SpaceX

Better, Cheaper Rides to Space

On December 21, 2015, SpaceX stuck the vertical landing of the first stage of its Falcon 9 rocket after successfully delivering 11 satellites into orbit. As SpaceX founder Elon Musk remarked at the time, "No one has ever brought an orbital class booster back intact. We achieved recovery of the rocket in a mission that also deployed 11 satellites. This is a fundamental step change compared to any other rocket that's ever flown."[2] It was a moment that captured the public's imagination like no other NewSpace mission had before.

While it did not have the seismic worldwide effects of Sputnik or Vostok or Mercury or Apollo, the success of the mission erased any doubt that a private company could successfully, and repeatedly, reach orbit. We glimpsed the future. We realized that we could deliver the stuff of NewSpace—the satellites, the ISS payloads, the as-yet-imagined craft—to orbit at a cost that would only serve to accelerate exploration, experimentation, and the NewSpace economy.

THE ECONOMICS OF LAUNCH VEHICLE REUSABILITY

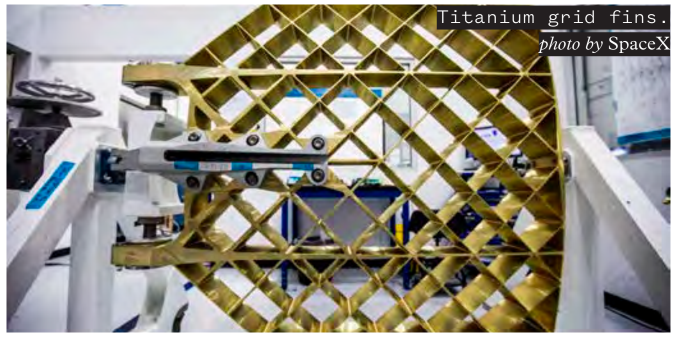
Traditional rockets are expendable—fly cargo into orbit and dump the booster that brought it there. Companies like SpaceX and Blue Origin don't see this as a viable long-term strategy. They are developing reusable rockets with hopes to reduce launch costs and accelerate the industry's pace of progress.

A SpaceX Falcon 9 launch, for example, costs approximately $62 million, while the comparable, but not reusable, United Launch Alliance Atlas V rocket costs approximately $109 million to launch.[3] These numbers can fluctuate, but overall, SpaceX, with its reusable Falcon 9, offers significantly more affordable rides to space.

According to early estimates, a Falcon Heavy, currently SpaceX's largest launch vehicle, will cost about two and a half times less to reach orbit than its closest competitor, the non-reusable United Launch Alliance Delta IV Heavy.

Blue Origin, while it has yet to launch its first reusable orbital rocket, has proven the capability of its suborbital New Shepard rocket and accompanying crew capsule to launch, land, and be reused on multiple flights.[4]

HOW TO LAND A ROCKET


Titanium grid fins.
photo by SpaceX

Landing a rocket is not unlike balancing a large broomstick vertically on the palm of one's hand—to succeed, there are hundreds of small movements that must be choreographed without fault. Now imagine that rocket was traveling at speeds over 6,000 km/h and had to come to a complete stop within five minutes. It's a profoundly difficult challenge.

To solve it, SpaceX developed a unique system of complementary controls, components, and processes.

The Falcon 9, SpaceX's flagship launch vehicle, is designed with an additional fuel margin so that the engines can be reignited multiple times to slow the rocket before it reaches the landing pad. These engines are also able to be gimbaled, enabling last-second corrective maneuvers.

In addition to the extra fuel, SpaceX has also equipped the Falcon 9 with nitrogen gas thrusters and foldable heat resistant wings known as grid fins. These fins help further steer the rocket to the landing target.

Unlike traditional grid fins, those on the Falcon 9 are bare titanium. While more expensive than their predecessor that used painted aluminum, titanium can withstand higher reentry speeds and requires less refurbishment (it doesn't require repainting with ablative material after each landing).

Carbon fiber landing legs are deployed seconds before landing, helping further stabilize the rocket on the pad. All of the SpaceX landing systems are automated and adjusted during each launch using real-time flight data.[5]

(2) Wall, Mike. "Wow! SpaceX Lands Orbital Rocket Successfully in Historic First." Space.com, Space.com, 22 Dec. 2015, www.space.com/31420-spacex-rocket-landing-success.html.
(3) Grush, Loren. "A Successful SpaceX Falcon Heavy Launch Gives NASA New Options." The Verge, The Verge, 2 Feb. 2018, www.theverge.com/2018/2/2/16954582/spacex-falcon-heavy-rocket-launch-impact-nasa-deep-space-travel.
(4) Burns, Matt, and Brian Heater. "Blue Origin Successfully Lands Both Booster and Crew Capsule after Test Launch." TechCrunch, TechCrunch, 18 July 2018, techcrunch.com/2018/07/18/blue-origin-successfully-lands-both-booster-and-crew-capsule-after-test-launch/.
(5) "GRID FINS." SpaceX, SpaceX, 1 Sept. 2015, www.spacex.com/news/2015/08/31/grid-fins.


Falcon Heavy reusable side boosters land in unison at Cape Canaveral Landing Zones 1 and 2 following test flight on 6 February 2018.
photo by SpaceX

LAUNCH RATE

In 2017, SpaceX President and COO Gwynne Shotwell stated that the company hopes to eventually achieve 30-40 launches annually (SpaceX flew 18 times in 2017 and has completed 16 successful commercial flights plus one test flight of Falcon Heavy in the first ten months of 2018 alone). To put those numbers in perspective, today there are approximately 80-90 orbital launches worldwide annually and there have been only around 5,400 launches since the beginning of the space age. SpaceX is consistently accounting for more and more of the global market share.

While large reusable rockets are topping launch headlines, other companies are working to develop new vehicles that cater specifically to the growing small satellite market.

DIVERSITY OF LAUNCH OPTIONS

Small satellites often hitch rides into space on launches dedicated to larger customers. A client with a large satellite will book a rocket and work with the launch provider to determine when that rocket launches and where it ultimately goes. Small satellite owners can purchase a ride on the same rocket in the remaining space (a strategy often referred to as "piggybacking" or ride sharing).

As the small satellite market grows, so does the market to design rockets specifically catered to its launch needs. American launch provider Rocket Lab is developing the Electron rocket, which is designed to send up to approximately 225 kg into low-earth orbit. Compare this to SpaceX's Falcon 9, which can carry approximately 22,800 kg to the same orbit.

Peter Beck, Rocket Lab's Founder, CTO, and CEO, notes that with Rocket Lab's Electron rocket, the small satellite owner will not have to compromise. "On a small rocket, they don't hitch a ride—they own the ride. That's the big difference. When you're a small rocket riding on a large launch vehicle, you just have to go where the bus goes. You're on someone else's time schedule, going to where the prime customer wants to go. Ride share works fine when you have a technology demonstration you want to throw up or an early stage spacecraft, but when you actually need to build a business in space and you need to deploy spacecraft to a particular orbit in a timeframe that makes commercial sense, then hitching a ride on a big rocket just does not work."

Trends in Satellite Manufacturing

Today's satellites have smartphones to thank for their ever decreasing size, ever-increasing capability, and ever greater affordability. As the smartphone market has become more competitive, its core technologies (batteries, cameras, accelerometers, radios, etc…) have become smaller and more capable. Now, NewSpace companies can purchase much of the technology they need off-the-shelf. And, because the core tech is already miniaturized, the satellites they build are smaller, lighter, and ultimately cheaper to launch into space.[7]

It is hard to overstate how different these new satellites are in both form factor and cost from their traditional counterparts. It was not unusual for satellites to cost hundreds of millions of dollars, take years to make, and be as large a school bus (and just as heavy).

As a result of this profound miniaturization, for the first time ever, NewSpace companies have the option to design a business around a fleet of satellites.

San Francisco-based Planet Labs uses a constellation of over 100 CubeSats to image the entire Earth every day. CubeSats are the industry standard for miniature satellites—they are 10x10x10 cm cubes (one cube is referred to as 1 unit or 1U). Planet Labs satellites, which the company refers to as "Doves," are 3U CubeSats.

Imaging our planet is not new, but the frequency of those images is. Planet Labs is providing the ability to watch the world change day over day, rather than year over year: a capability that has garnered interest from the agriculture and maritime industries, governments, and media.

Farm owners, for example, often use a combination of multi-spectral imagery from satellites (resolution as good as five feet per pixel) for overall analysis of larger farms as well as the high-resolution imagery (two feet per pixel) from terrestrial drones to hone in on certain areas.

At its factory in San Francisco, Planet Labs can produce up to 40 Doves per week—a satellite manufacturing achievement unheard of in the space industry. Having the capability to rapidly produce satellites allows the startup to quickly update their fleet with new technologies and capabilities.

Will Marshall, Co-founder and CEO of Planet Labs, notes, "You can imagine that if you spent 10 years building one $500 million satellite, failure is simply not an option. By using the same technology found in smartphones, we are able to build smaller satellites that are highly capable yet very affordable. As a result, we build many more and take more risks, knowing that if one or two fail, it's not a big deal."

In 2014 and 2015, Planet Labs lost 34 total satellites due to launch vehicle failure. To lose 34 satellites within one year would have killed most NewSpace businesses, but because those satellites were relatively easy to replace, Planet Labs survived this setback. Today, the company operates the largest satellite constellation in history.[8]

The data gathered by satellite imaging companies like Planet Labs is of little use without interpretation and analysis. A select group of software startups is out to do just that. Orbital Insight, Descartes Labs, Ursa Space Systems, and SpaceKnow use AI to drive insights into everything from retail foot traffic to urban development and crop health.

INTERNET FROM ORBIT

The idea of internet from space is not new. Satellite internet has been pursued for decades, but as with other commercial space ventures, the traditional approaches were stifled by their era's technology.

Today, satellite internet start-ups have billions of dollars' worth of investments. It is one of the largest funded sectors in the NewSpace industry. Why? Because satellites and launches are cheaper than ever before.

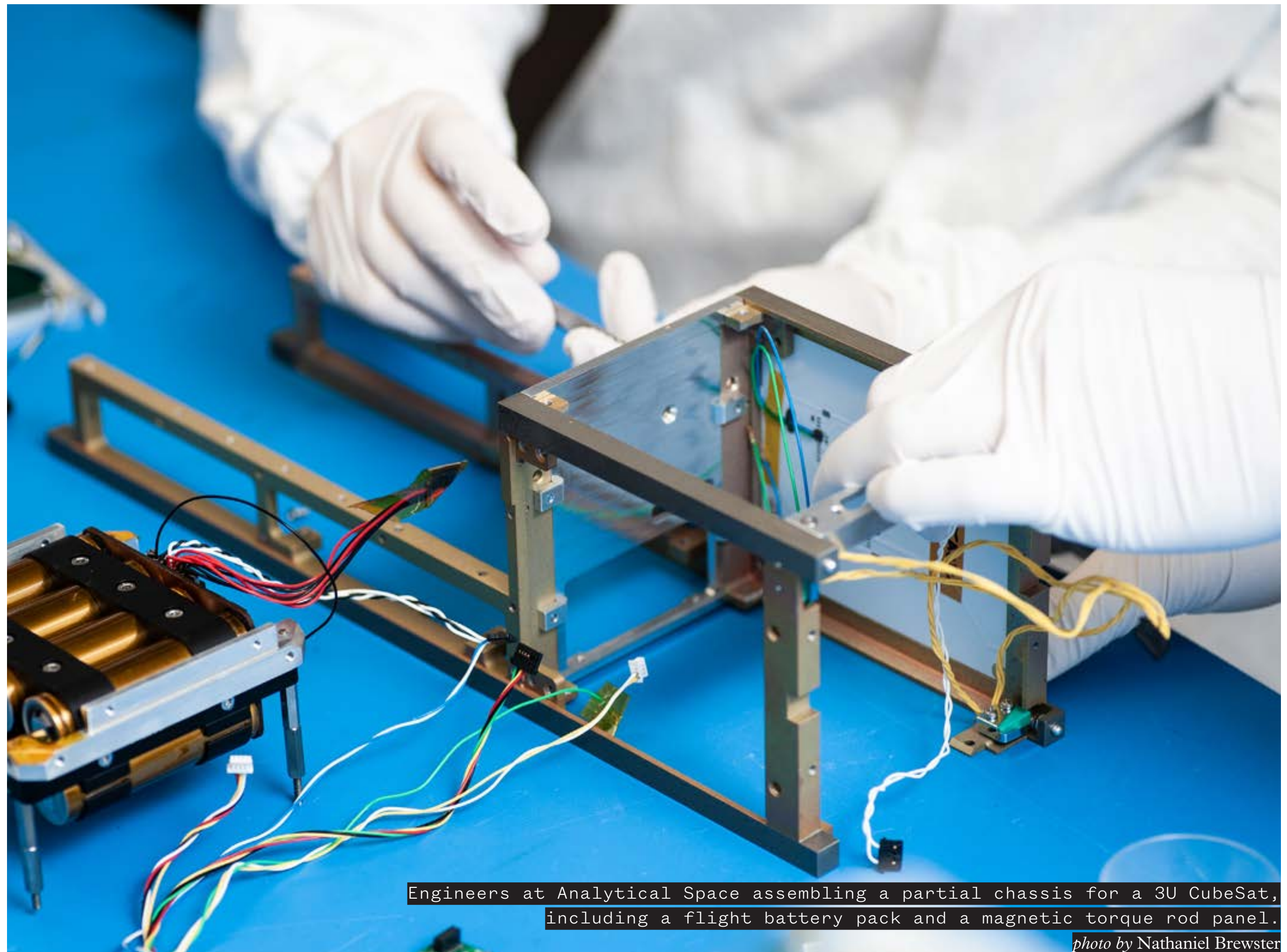
Previous satellite internet pursuits were located in high orbits and were only able to provide high-latency (slow) internet to select areas. To supply low-latency broadband internet, a satellite constellation must be built in low-Earth orbit. While satellites in such an orbit can provide internet without much delay, they only see one small swath of the world at any given moment. To solve this problem, a constellation of hundreds, or potentially thousands, of satellites is needed.

(Such a concept was attempted before. In 1994, Microsoft-backed Teledesic proposed launching nearly 800 satellites to deliver global broadband internet. Costs and terrestrial competition proved to be too much and Teledesic's satellite construction halted in 2002.)

OneWeb plans to launch hundreds of satellites into low-earth orbit and bring faster-than-broadband internet to the world. The company has started construction on its proposed fleet of 1,980 satellites and has currently raised approximately $2 billion.[9]

SpaceX has a similar proposal called Starlink, though the estimated size of its satellite constellation is over 11,900.[10] In April of 2018, Gwynne Shotwell estimated that it would cost around $10 billion to deploy this fleet of satellites.

But success for OneWeb or Starlink is not just predicated upon a sound investment strategy. Dozens of enabling technologies must be refined enough to ensure consistent, profitable, launch and operations. Dependence on those technologies poses a fundamental risk for the satellite internet business model, as well as other space-based ventures.



Engineers at Analytical Space assembling a partial chassis for a 3U CubeSat, including a flight battery pack and a magnetic torque rod panel.
photo by Nathaniel Brewster

Justin Oliveira, CEO & Co-Founder; Dan Nevius, COO & Co-Founder, Analytical Space.
photo by Doug Levy.

(7) Argent, Anne-Wainscott. "Smaller Is Better How Small Satellites Have Become a Compelling Option - Via Satellite-." Via Satellite, Via Satellite, 21 Aug. 2013, www.satellitetoday.com/government-military/2011/07/01/smaller-is-better-how-small-satellites-have-become-a-compelling-option/.
(8) "Planet Labs Targets a Search Engine of the World." NASASpaceFlight.com, www.nasaspaceflight.com/2018/01/planet-labs-targets-search-engine-world/.
(9) "OneWeb Asks FCC to Authorize 1,200 More Satellites." SpaceNews.com, 20 Mar. 2018, spacenews.com/oneweb-asks-fcc-to-authorize-1200-more-satellites/.
(10) Brodkin, Jon. "FCC Tells SpaceX It Can Deploy up to 11,943 Broadband Satellites." Ars Technica, Ars Technica, 15 Nov. 2018, arstechnica.com/information-technology/2018/11/spacex-gets-fcc-approval-for-7500-more-broadband-satellites/.

The Manufacturing Techniques and Materials of NewSpace

ADDITIVE MANUFACTURING

We have entered the age in which aerospace parts, the flight hardware that helps propel rockets into orbit, can be printed. The maturation of metal-based 3D printing techniques and material science advancement in metal alloys have enabled NewSpace companies to use this technology, once relegated solely to the realm of prototypes, for production of aerospace-grade components.

The advantages of additive manufacturing are many. Aside from reducing the number of welding points, which reduces costs, production time, and potential failure points, 3D printing wastes significantly less stock compared to its subtractive manufacturing counterparts, further cutting production costs.

In 2015, NASA printed its first full-scale copper rocket engine part. While copper is extremely good at conducting heat, making it particularly useful within the lining of a combustion chamber, it is this same property that makes it difficult to melt during the 3D printing process. To solve this problem, NASA invented a new copper-alloy known as GRCo-84—a powder that can be melted continuously for 3D printing, and maintain the conduction properties necessary for a rocket engine's combustion chamber.

Copper may be an excellent thermal conductor, but it is relatively weak compared to other metals. For this reason, NASA developed a 3D printing process called E-Beam Free Form Fabrication Technology, which deposits a nickel-alloy on top of the copper-alloy liner using an electron beam and solid wire feedstock.

Rocket Lab, a launch company developing relatively small rockets for the small satellite market, is 3D printing most of its primary rocket engine. The company uses a process known as electron beam melting, which, like NASA's technology, harnesses an electron beam. But they instead use this beam to melt metal powder.

Nine of Rocket Lab's 3D printed Rutherford Engines bring 150 kN of liftoff thrust to the Electron first stage while a single Rutherford Engine provides 22 kN of thrust to its second stage. According to Rocket Lab, the company can print the engine in just 24 hours—a staggering achievement.

Relativity Space, a company also developing small launch vehicles, wants to go even further by 3D printing an entire rocket. Founders Tim Ellis and Jordan Noone—former SpaceX and Boeing engineers—are on a mission to reduce the number of moving parts in its company's rocket, increasing its mechanical efficiency and reducing the number of potential failure points. NASA's Space Shuttle had an estimated 2.5 million parts. The duo's stated goal is to create a 3D-printed rocket with just 1,000 moving parts. But to do that, the company had to build its own specialized metal powder-fed 3D printer known as Stargate.[11]

Stargate, which the company claims is the world's largest metal 3D printer, is powered by three robotic arms and is capable of printing 95% of Relativity Space's Terran 1 rocket in a proprietary high-strength aluminum alloy.

Relativity Space has raised more than $45 million in venture funding and an estimated $1 billion worth of nonbinding launch term sheets and letters of intent. The company plans to test its Terran 1 rocket in 2020.[12]

3D-printed copper combustion chamber.
photo by: NASA/MSFC/Emmett Given

(11)Nasa. (2015) Dawn at Ceres.
(12)"TILE." Accion Systems - A New Ion Engine, www.accion-systems.com/tile/.

Natalya Bailey, Co-Founder & CEO, Accion Systems.
photo by Accion Systems

PROPULSION

Until recently small satellites had no method of propulsion while in orbit. Their lives were short—many only lasted months or a few short years in orbit before succumbing to atmospheric drag and burning up. If the small satellite revolution is to truly take root, small satellites must have a reliable and capable propulsion system.

Natalya Bailey, the founder and CEO of Accion Systems, a startup working to bring propulsion to small satellites for the first time, reflects on the advantages of such a system, "When a small satellite has positioning capabilities from a propulsion system, its mission lifetime is greatly extended meaning that fewer satellites need to be launched and one satellite can perform multiple tasks."

The company is building miniature ion thrusters, each about the size of a quarter, using technology originally developed at MIT. These thrusters are inherently different than traditional ion engines used on today's spacecraft.

The Dawn mission to the Vesta asteroid, for example, was powered by three traditional ion engine thrusters measuring 30.5 cm in diameter and 33 cm in length.[13] These thrusters provided 91 mN of thrust. Accion's thrusters, on the other hand, are only 3x7x12 cm in there smallest configuration and can provide .05 mN of thrust, enough to propel a spacecraft up to 200 kg.[14,15]

Accion uses a different source of ions—a salty liquid propellant—in its thrusters, instead of compressed gasses like that of traditional ion engines. This allows them to avoid the use of large chambers and valves, pressurized tanks, and external cathodes.

A postage stamp sized thruster chip.
photo by Accion Systems

(13)"Dime-Size Thrusters Could Propel Satellites, Spacecraft." Space.com, Space.com, 23 Mar. 2017, www.space.com/36180-dime-size-accion-thrusters-propel-spacecraft.html.
(14)Campbell, Ashley. "Optical Communications." NASA, NASA, 16 Oct. 2017, www.nasa.gov/directorates/heo/scan/opticalcommunications/.

LASER SYSTEMS

Like propulsion, there are technologies poised to take advantage of the NewSpace industry's most fundamental platforms, while providing them with greater, more useful capabilities.

One Boston-based company, Analytical Space, gives companies in industries from agriculture to consumer goods the ability to harness data gathered in orbit at near real time. The current data transfer paradigm looks like this: data is "stuck" in orbit until a satellite is physically positioned over a particular ground station, only then can the satellite send its data—it's all about line of sight.

Analytical Space aims to solve this problem with dozens of shoebox-size relay satellites. If a company wants to bring its data down quickly, but the satellite isn't yet in the field of view of its ground station, they could "pass" that data to a well-positioned satellite owned by the startup to get its data down faster.

Analytical Space plans to transfer data through a mix of radio and laser waves. Laser-based technology for telecommunications is particularly attractive because the optical wavelength is capable of 40 times higher data rates than radio frequencies. Optical communication systems are also lighter and more secure.[16]

But laser transmission is not without its tradeoffs. Unlike radio waves, which can be sent out in a broad beam covering a large area, a laser's narrow beam width requires more precise positioning, especially when trying to communicate with a ground station hundreds of kilometers away. And while radio waves can be used to transfer data through all types of atmosphere, laser waves have issues with clouds and mist, requiring either the vacuum of space or clear skies to operate.[17]

With a mix of radio and laser systems, Analytical Space hopes to accommodate all weather scenarios as well as clients' satellite and ground station capabilities.

DEALING WITH SPACE DEBRIS

Tracking systems have identified approximately 20,000 pieces of space debris larger than a softball orbiting the Earth today. These include defunct satellites; discarded equipment and rocket stages; remnants left over from an anti-satellite test conducted by China in 2007 that created more than 3,000 pieces of trackable debris; and an accidental collision between American and Russian communication satellites in 2009 that generated over 2,000 pieces of trackable debris. Statistical models, however, estimate that more than 500,000 pieces of human-made debris larger than a marble and millions of pieces as small as a fleck of paint are also in orbit.

These pieces are travelling at speeds of 28,163 km/h, fast enough to damage spacecraft and satellites. Because of this, the US military-operated Space Surveillance Network tracks debris at all times and notifies spacecraft owners if any are potential threats.

In 2017, the Space Surveillance Network had over 300,000 instances of notable concern of debris impacting a spacecraft. 655 of those events were emergency reports, 579 of which were in low-earth orbit.[18]

The challenge of orbital debris will only become more complex as a greater number of spacecraft are stationed around the Earth. Current methods of altering final orbits or allowing a spacecraft to succumb to natural orbital decay do not scale well—especially when a satellite goes defunct before it can initiate its end-of-life plan

This is why a team at the University of Surrey in London is developing a project called RemoveDEBRIS to launch a net capable of capturing defunct spacecraft. After capturing the satellite with a net, the team could either deploy a drag sail (a large membrane that increases aerodynamic drag), or launch a tethered harpoon with the net and reel in the satellite.

RemoveDEBRIS has been testing its net technology for six years on parabolic flights (airplane flights that simulate a weightlessness). This year, the team completed its first successful in-flight net deployment and satellite capture. Over the next year, the company will begin to test its cameras and LIDAR technology to identify orbital debris, its harpoon technology, as well as its drag sail.

The Radix CubeSat being launched from the ISS.
photo by Analytical Space.

(15)Campbell, Ashley. "Optical Communications." NASA, NASA, 16 Oct. 2017, www.nasa.gov/directorates/heo/scan/opticalcommunications/.
(16)Mosher, Dave. "The US Government Logged 308,984 Potential Space-Junk Collisions in 2017 - and the Problem Could Get Much Worse." Business Insider, Business Insider, 15 Apr. 2018, www.businessinsider.com/space-junk-collision-statistics-government-tracking-2017-2018-4.
(17)NASA, www.nasa.gov/mission_pages/station/research/experiments/explorer/Investigation.html.

The Policies That Help Make NewSpace Possible

Recent policy initiatives are undeniably influencing the direction in which the NewSpace industry is moving. These policies include government programs that subsidize the development of certain space companies, as well as new laws passed to clarify rules around space-based initiatives.

Both NASA and the Department of Defense have shown a keen interest in helping certain NewSpace companies succeed.

For over a decade, NASA has facilitated the development of orbital rockets and space capsules at SpaceX, Orbital ATK (recently acquired by Northrop Grumman), and the Sierra Nevada Corporation via contracts awarded through two primary programs: Commercial Orbital Transportation Services and Commercial Resupply Services. NASA benefits from these programs by having American-made rides to the International Space Station, while these companies benefit from having the government as a guaranteed customer for a certain number of flights. In fact, in 2016 government customers provided 70% of the revenues for orbital launches of satellites.[20]

As John Logsdon, Former Space Policy Director at George Washington University, observes, "The government interest in NewSpace is multifold. Creating new business stimulates the economy and creates more tax revenue. Also, many of these new technologies help the government carry out its own business, like cheaper access to space for example."

NASA subsidized the development of human-rated orbital rockets and capsules at SpaceX and Boeing through contracts via the Commercial Crew Program. A particularly important initiative considering once the Space Shuttle retired in 2011, NASA began paying the Russians to send American astronauts into space. From 2011-2018, NASA paid the Russians over $3 billion for these rides.[21] In recent years, NASA has paid as much as $81.6 million per seat, so one can imagine the incentive to develop American-made rides quickly.[22]

The DOD also has a vested interest in the United States excelling in launch technology, specifically on-demand launch services that can quickly replace military assets in orbit. Recently, the Air Force proposed a small launch services program that would distribute $192.5 million over the course of five years to new launch providers like Virgin Orbit and Stratolaunch.

Air Force Secretary Heather Wilson has said that the goal of this program is to "have a variety of launch capabilities in order to have assured access to space."

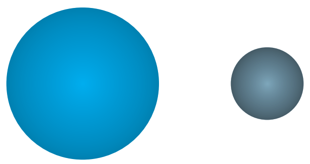
While these companies have yet to fly commercial payloads, Virgin Orbit and Stratolaunch are interesting to the DOD because the companies' launch strategy may enable faster access to space over the rocket companies available today. Instead of launching a rocket from a launchpad, these two companies fly rockets up to 35,000 feet with specially modified airplanes and launch them mid-air.

This strategy has two key benefits: a payload can be launched virtually anywhere in the world as long as it has a large enough runway, and perhaps more importantly they can avoid one of the most common delays for rocket launches: weather. /

(18)Bryce Space and Technology. (2017) 2017 State of the Satellite Industry.
(19)Messier, Doug. "NASA's Commercial Crew Program By the Numbers." Parabolic Arc, www.parabolicarc.com/2016/10/24/nasas-84-billion-commercial-crew-program/.
(20)Grush, Loren. "NASA Coughs up $490 Million for Six More Seats on Russia's Soyuz Rocket." The Verge, The Verge, 6 Aug. 2015, www.theverge.com/2015/8/6/9108703/nasa-buys-seats-russia-soyuz-rocket-490-million.
(21)"Pentagon Budget Funds 'Small Launch Services' to Gain Greater Access to Space." SpaceNews.com, 15 Feb. 2018, spacenews.com/pentagon-budget-funds-small-launch-services-to-gain-greater-access-to-space/.

The NewSpace Market

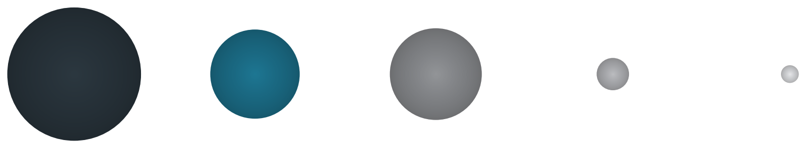
THE SPACE INDUSTRY



350 BILLIONS Space Industry

79.3 BILLIONS Government Budgets & Commercial Human Spaceflight

THE SATELLITE INDUSTRY



268.6 BILLIONS Satellite Industry

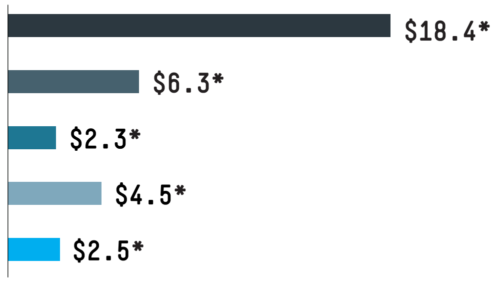
119.8 BILLIONS Network Equipment & Consumer Equipment

126.7 BILLIONS Telecom, Earth Observation, Science, National Security Worldwide

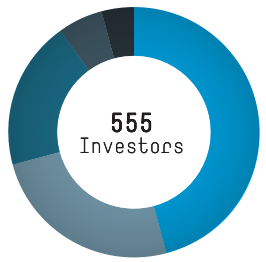
15.5 BILLIONS Satellite Manufacturing

4.6 BILLIONS Launch Industry

START-UP SPACE INVESTMENTS SINCE 2000



INVESTORS IN START-UP SPACE COMPANIES SINCE 2000



START-UP COMPANIES WORLDWIDE

195 Worldwide

130 Are located in the US

47 Are located in California

Leading NewSpace Companies

Accion Systems is developing high-quality, affordable propulsion technologies that enable increased access to space. Its postage-stamp size ion engines will help meet even the most challenging propulsion requirements for CubeSats, GEO satellites, or even interplanetary missions.
Founder, CEO: Natalya Bailey | Founder, Chief Scientist: Louis Perna

Analytical Space is building an orbital network of shoebox-size relays to help data-gathering satellites get more information to the ground, faster, without any changes to existing hardware.
Founder, CEO: Justin Oliveira | Founder, COO: Dan Nevius | CTO: Abdul Mohsen Al Husseini | CFO: Tanveer Kathawalla

Blue Origin is a manufacturer of orbital and suborbital reusable rocket systems. The company aims to pioneer space tourism with its New Shepard rocket system, and carry people and payloads into space aboard the New Glenn heavy-lift launch vehicle. It also manufactures rocket engines used by other NewSpace launch providers.
Founder: Jeff Bezos | CEO: Bob Smith

DigitalGlobe operates a satellite constellation that provides high-resolution Earth imagery. The company uses cloud-based platforms to analyze this imagery and provide corporations and governments with the insights to make sound critical decisions.
President: Dan Jablonsky | CTO, Exec. VP: Dr. Walter Scott

ICEYE operates the first satellite under 100kg to carry synthetic-aperture radar (SAR). Its technology helps create images of the Earth that are unaffected by weather and time of day. It is developing a constellation of SAR-enabled satellites in conjunction with the European Space Agency.
CEO, Founder: Rafal Modrzewski | CSO, Founder: Pekka Laurila

OneWeb is producing a constellation of 1,980 satellites that will provide the planet with high speed, broadband internet access. It is also producing ground-based user terminals that will transmit the satellite signals to a user's device via WiFi/LTE/3G and 2G radios.
Founder: Greg Wyler | CEO: Adrian Steckel

Planet Labs created, launched, and manages a constellation of Earth-imaging Triple-CubeSats (3U) that image the entire Earth every day. The company's monitoring and analytics platforms help customers interpret and act upon these images as they happen.
Founder, CEO: Will Marshall | Founder, Chief Strategy Officer: Robbie Schingler

Relativity Space is pioneering an autonomous rocket factory and launch service. It is spearheading massive-scale, metal 3D printing to create the world's first 3D-printed rocket.
Founder, CEO: Tim Ellis | Founder, CTO: Jordan Noone

Reaction Engines is engineering an air-breathing rocket engine for reusable launch vehicles that can be used both in the air and in the vacuum of space. Its technology, which combines the fuel efficiency of a jet engine with the power and speed of a rocket, will enable a new generation of capabilities for air and space vehicles.
COO, Engineering Director: Mark Wood
CTO, Chief Engineer: RIchard Varvill

Rocket Lab creates expendable launch vehicles for small satellites. Its rocket, the Electron, is made from carbon composites and uses a 3D-printed engine. The company aims to mass produce rockets and bring launch customization to the small satellite customer.
CEO, CTO, Founder: Peter Beck

SpaceX is a pioneer in the reusable launch vehicle market. The company has successfully reused more than 12 first stage boosters. In 2019, SpaceX plans to fly its first humans into orbit. The company is also pursuing satellite internet and the prospects of creating a settlement on Mars.
CEO: Elon Musk | COO: Gwynne Shotwell
CTO of Propulsion: Tom Mueller

Spire Global is a data and analytics company powered by a constellation of small satellites. These satellites cover portions of the globe that often remain untracked due to accessibility issues; its data helps empower maritime, weather, and aviation industries with unique and actionable insights.
Founder, CEO: Peter Platzer | Founder, CTO: Joel Spark | Founder, CTO: Jeroen Cappaert

SpinLaunch is designing a catapult system to launch small satellites into space. Using the momentum from a fast-spinning centrifuge to fling payloads into orbit, the company will remove the need for chemical propellants, reducing launch costs dramatically.
Founder, CEO: Jonathan Yaney

Stratolaunch is building the world's largest plane in order to launch vehicles at an altitude of 35,000 ft. The carrier aircraft is capable of carrying a variety of rockets and a space plane which will bring payloads of up to 6,000 kg and eventually crew the rest of the way to orbit.
Founder, Chairman: Paul G. Allen | CEO: Jean Floyd

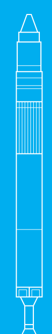
Vector is creating launch vehicles solely for the burgeoning small satellite market. The company's rocket design enables frequent and reliable access to space, at prices that should empower satellite-startups to send more to space, more often.
Founder, CEO: Jim Cantrell | Founder, President of Launch Services: John Garvey | Founder, CTO: Eric Besnard | Founder, Chief Sales and Marketing Officer & SVP/GM GalacticSky: Shaun B. Coleman

Virgin Orbit is developing a mobile air-launch system using a modified 747 airplane (named Cosmic Girl) to carry its LauncherOne rocket to 35,000 ft. The rocket will ignite mid-air and carry a payload of up to 500 kg to orbit. Cosmic Girl can theoretically take off on any runway that can accommodate a 747, enabling customers to reach many orbital inclinations. Thanks to hybrid additive-subtractive manufacturing, Virgin Orbit can manufacture around 24 of its rockets per year.
President, CEO: Dan Hart

Landmarks in NewSpace

2005 — NASA Administrator Mike Griffin challenges U.S. private industry to develop space transportation capabilities that could meet the needs of the ISS

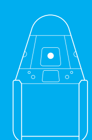
2006 — NASA establishes Commercial Orbital Transportation Services (COTS) program



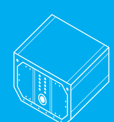
2008 — SpaceX Falcon 1 becomes the first privately-developed liquid-fuel launch vehicle to reach orbit

2010 — SpaceX publishes its launch prices

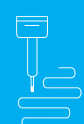
NanoRacks launches platform to the ISS and becomes the first commercial laboratory in space



2012 — SpaceX Dragon berths with ISS, becoming the first commercial space vehicle to do so

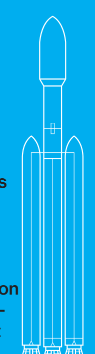


2013 — SpaceX successfully launches first commercial satellite into orbit



2014 — Made In Space 3D prints the first object in space on board the ISS

2015 — SpaceX lands its Falcon 9 orbital booster for the first time

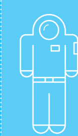


2017 — FCC grants OneWeb approval to launch an initial constellation of 720 low-Earth orbit satellites

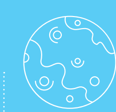
2018 — SpaceX successfully launches Falcon Heavy, recovering two of the three first stage boosters

Blue Origin successfully launches and lands its New Shepard rocket for the ninth time

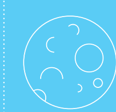
Rocket Lab performs first commercial launch of its Electron rocket, deploying 6 small satellites into orbit



2019 — SpaceX plans to launch their first humans into space with the Falcon 9 rocket



2022 — SpaceX aims to send first cargo mission to Mars



2024 — Blue Origin plans moon landing

Data from: Bryce Space and Technology, 2018 State of Satellite Industry.

The Portfolio Companies

We invest in the transformative, the audacious, and the new. These 14 companies—and the founders they represent—are working on scientific breakthroughs and converging technologies that hold the potential to redefine the future.

Analytical Space
Space & Internet of Things

C2Sense
Advanced Materials & Internet of Things

Cambridge Electronics
Semiconductors

Cellino Biotech
Biotech & Life Sciences

Commonwealth Fusion Systems
Energy

E25Bio
Biotech & Life Science

Form Energy
Energy

HyperLight
Advanced Materials

ISEE
Deep Software & AI

Kytopen
Biotech, Life Sciences & Advanced Manufacturing

RadixBio
Robotics, Deep Software, Internet of Things, Biotech & Life Sciences

Suono Bio
Biotech & Life Sciences

Via Separations
Energy, Advanced Materials & Advanced Manufacturing

Zapata Computing
Quantum Computing Software

E25Bio

Founders	|1| Irene Bosch; Lee Gehrke
Background	MIT, Harvard, Genzyme, Sanofi
Industry	Biotech & Life Sciences

E25Bio has developed a rapid, point-of-care infectious disease response system that detects mosquito-borne infectious diseases in minutes, while providing public health officials with the data to pinpoint infected areas.

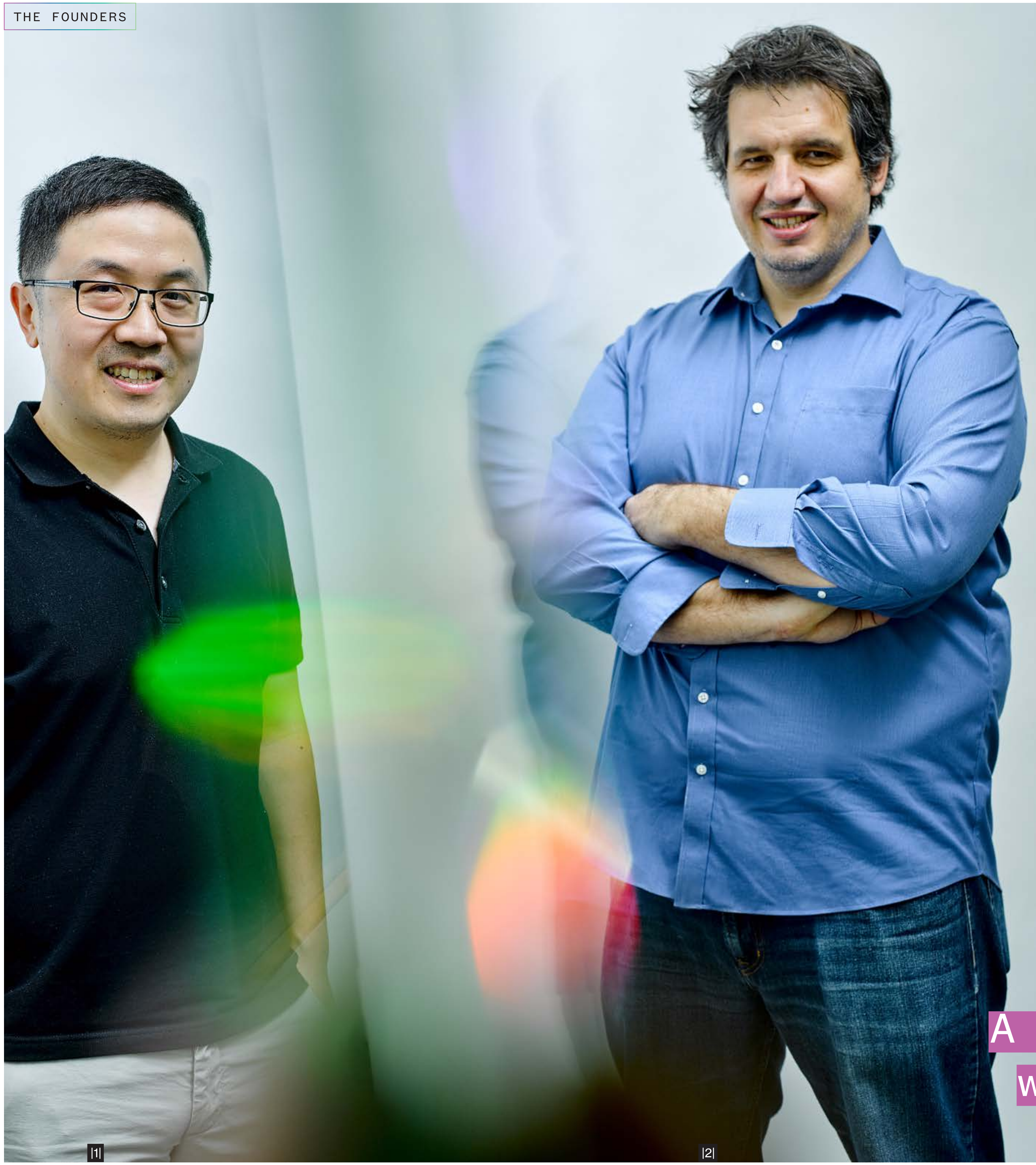
The test, a nitrocellulose diagnostic strip (similar to those found in over-the-counter pregnancy tests), was engineered for its accuracy and affordability.

Though the form factor may be simple and affordable, it is a vehicle for something far more valuable: antibodies. E25Bio has developed the first test of this kind to distinguish between dengue (as well as all four subtypes of the disease), chikungunya, and Zika. The lack of cross-reactivity in the test will help eliminate misdiagnosis and inaccurate or insufficient treatment.

E25Bio has worked with image recognition experts to create a mobile-based platform to catalog the results of their test along with corresponding time and location. The data will be used by local governments to create a near real-time portrait of a potential epidemic and take necessary preventative measures while the spread of disease is still controllable.

E25Bio's infectious disease response system will empower patients, healthcare workers, and public health officials to stem the spread of a potential epidemic, wherever it may strike. Disease, after all, knows no borders.

Pioneering a rapid, point-of-care response system for deadly infectious diseases.



HyperLight

Founders	**|1|** Mian Zhang, **|2|** Marko Loncar, Cheng Wang
Background	Laboratory for Nanoscale Optics at Harvard University
Industry	Advanced Materials

From the confines of a quantum computer, to data centers, to nondescript cables spanning our oceans or threaded beneath our city streets, optical fiber enables instant and profound connectivity.

The connections between our most fundamental technologies rely on a device to convert signals between electricity and light waves at high speeds: the electro-optic modulator.

Electro-optic modulators made with Lithium Niobate (LN) are the most common due to LN's long-known ability to efficiently convert between electrical and optical domains. However, LN has remained difficult to fabricate on the chip scale using microfabrication processes, which has left electro-optic modulators in bulky, discrete, expensive forms that cannot scale, integrate with CMOS electronics, or achieve certain performance metrics. Photonics platforms based on other materials do provide on-chip integration, but come with performance trade-offs due to non-ideal material properties.

HyperLight has unlocked a foundational way to achieve both unprecedented performance and scalability from LN.

The team of Mian Zhang, Cheng Wang, and Marko Loncar, through work out of the Laboratory for Nanoscale Optics at Harvard University, discovered a method of fabricating integrated, chip-scale LN modulators with extremely low signal loss. These devices are key enablers for the future of data communications, adding exponentially more capacity and speed, while consuming significantly less power than their traditional counterparts.

A chip, powered by light, with the power to change everything.

Radix Labs

Founder	|1| Dhash Shrivathsa
Background	Olin College, MIT Media Lab
Industry	Robotics, Deep Software, Internet of Things, Biotech & Life Sciences

For all the wonders of its science, today's biology lab is inefficient and prone to human error. Its incredible machines, the equipment tasked with unlocking some of life's most profound mysteries, don't talk to each other. Humans perform repetitive tasks by hand without precise documentation. Reproducibility of results by peers is difficult or impossible.

Radix Labs is driven by the central belief that a biology lab is not just a series of disconnected steps and parts, but a very big and very real computer. And every computer needs a programming language. In Radix's case, its declarative programming language unites scientist and lab machinery in one automated unit. The software Dhash Shrivathsa created translates a typical lab protocol into a runnable program that systematically manages disparate laboratory machines and human tasks.

Radix Labs designed its software to be as accessible and fluid as possible—it had to work within the existing infrastructure of the lab and empower, not intimidate, its users. By distancing the specification of the program—in this case the lab protocol—from the execution, Radix Labs hopes to reduce a biologist's time in the lab, giving them more time to focus on experimental design and analysis.

Creating a universal operating system for biology labs.

|1|

Analytical Space

Founders
Justin Oliveira, Dan Nevius

Background
NASA, Planetary Resources, White House, HBS

Industry
Space & Internet of Things

Analytical Space is building a network of in-orbit communication relay satellites that use laser communication to offer expanded connectivity for data transfer, without any change to existing hardware. This results in faster data downloading, more access to download windows, lower latency, and improved cost structures, while being compatible with heritage satellites and new satellites alike.

Impact
Analytical Space will liberate and deliver terabytes of untapped data gathered by hundreds of satellites, giving humanity a more informed and dynamic picture of everything from industrial agriculture to weather.

Cambridge Electronics

Founders
Bin Lu, Tomas Palacios

Background
Microsystems Technology Laboratories MTL, Department of Electrical Engineering and Computer Science EECS

Industry
Semiconductors

Modern-day electronics rely on silicon processing, but Cambridge Electronics aims to bring a revolutionary semiconductor material to power electronics and communications based on their proprietary gallium nitride (GaN) technology. The company's proprietary technology is targeted to bring energy savings to electronics for data centers, electric cars, 5G communication, consumer devices— the entire energy processing landscape.

Impact
Cambridge Electronics is transforming a fundamental and ubiquitous technology to help power an exponentially more efficient and exciting future.

Cellino

Founders
Nabiha Saklayen, Stan Wang, Matthias Wagner, Marinna Madrid

Background
Harvard Physics Department, Harvard School of Engineering and Applied Sciences (SEAS), Harvard Medical School, The Church Lab

Industry
Biotech & LifeSciences

The cell therapy industry has great promise to enable the future of medicine, but currently has a massive supply chain problem. Cellino is solving this problem by applying its novel mix of nanotech, optics, and biology to stem cells. Their proprietary delivery technology "digitally steers" stem cells to differentiate, creating any cell type at will.

Impact
Cellino's platform for the high-throughput digitization of engineering human cells will transform the biotech industry, making cell-based therapies a staple of 21st-century medicine.

Commonwealth Fusion Systems

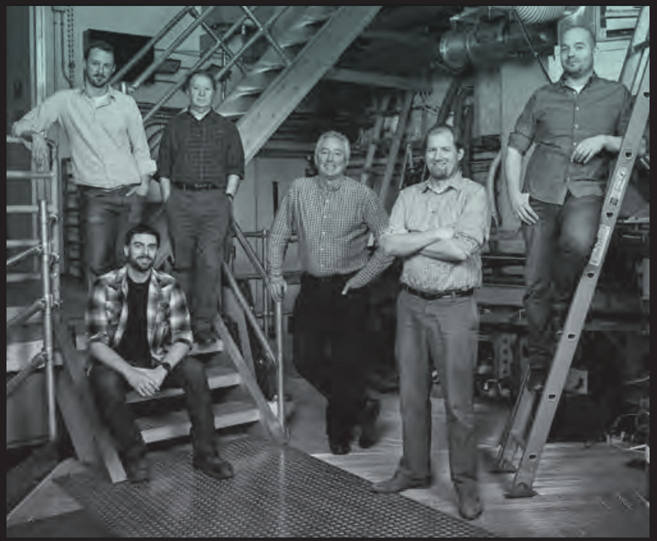
Founders
Zach Hartwig, Brandon Sorbom, Martin Greenwald, Dennis Whyte, Bob Mumgaard, Dan Brunner

Background
MIT Plasma Science and Fusion Center

Industry
Energy

Commonwealth Fusion Systems (CFS) aims to provide a new path to fusion power by combining proven fusion physics with revolutionary magnet technology to deploy the first working, economic fusion reactors to the world. The team will develop superconducting magnets based on a new class of high temperature superconductor materials that allow fusion reactors to be 10 times smaller, economically feasible, and operational in the next 10 years.

Impact
Fusion energy is the holy grail of clean energy: limitless, no greenhouse gases, baseload, concentrated, no meltdown, and no proliferation. If successful, the world's energy systems will be transformed.



C2Sense

Founders & Leadership
Jan Schnorr, Tim Swager, Eric Keller, George Linscott

Background
Tim Swager Lab MIT

Industry
Advanced Materials & Internet of Things

A digital olfactory sensor platform for industry, C2Sense's technology transforms smell into real-time data that can be accessed remotely. With high-fidelity electrochemical sensors at a low price point, C2Sense will empower a broad array of industries including those involved in food supply, power generation, and chemical production to take control of their environments.

Impact
By making gases detectable and trackable on an industrial scale, C2Sense reduces waste, improves safety and health of employees, and builds a more efficient and productive world.

Form Energy

Founders
Yet-Ming Chiang, Mateo Jaramillo, Ted Wiley, William Woodford, Marco Ferrara

Background
DMSE MIT, 24M Technologies, A123, Tesla Energy

Industry
Energy

Form Energy will solve large-scale renewable energy's most fundamental limitation—reliability—through energy storage. Rather than thinking of batteries in the traditional sense, simply as storage vessels, Form is designing bidirectional power plants. Built to displace fossil fuel baseload generation plants, Form Energy's core technology will store and supply hundreds of megawatts via the existing energy grid.

Impact
Form Energy will help usher in a future of humanity's baseload energy from renewable, clean wind and solar power.

ISEE

Founders
Yibiao Zhao, Debbie Yu, Chris Baker

Background
MIT Computational & Cognitive Science Group

Industry
Deep Software & AI

ISEE is engineering next-generation, humanistic AI for autonomous vehicles. Their cognitive core can reason through an uncertain future without sole reliance on hand-coded rules or rote pattern recognition. ISEE uses predictive modeling, theory of mind, and probabilistic reasoning to create the cognitive core.

Impact
Built on a cognitive core, ISEE's technology will usher in a world of safe autonomous vehicles, operating without accident and without the need for human intervention.

Kytopen

Founders
Paulo Garcia, Cullen Buie

Background
Mechanical Engineering MIT

Industry
Biotech & Life Sciences, Advanced Manufacturing

Kytopen aims to improve the efficiency of the genetic engineering of cells, regardless of the application. With its microfluidic-based tool, the company can accelerate and automate the genetic engineering of cells 10,000x times faster than current methods.

The technology also enables continuous flow genetic manipulation of cells in a platform that can be easily automated and can be used to process both small and large sample volumes.

Impact
The startup's non-viral Flowfect™ solution will reduce the cost and accelerate time to market for discovering and manufacturing next-generation cell and gene therapies.

Suono Bio

Founders & Leadership
Carl Schoellhammer, Robert Langer, Amy Schulman, Gio Traverso, Lisa Ricciardi

Background
Langer Lab MIT

Industry
Biotech & Life Sciences

Suono Bio has reimagined ultrasound as a effective and elegant delivery mechanism for the most delicate therapeutics. Its technology can push molecules like DNA, RNA, and proteins directly into cells without disrupting the surrounding tissue or harming the molecule itself. The flexibility and efficacy of the Suono Bio therapeutic platform brings with it the potential to treat and cure diseases with targets once deemed undruggable.

Impact
Suono Bio will more effectively treat challenging chronic gastrointestinal diseases and enable new therapies for other pressing health challenges like diabetes, cancer, and viral infections.

Via Separations

Founders
Shreya Dave, Brent Keller, Jeff Grossman

Background
The Grossman Group MIT

Industry
Energy & Advanced Materials, Advanced Manufacturing

12% of all US energy consumption is spent separating chemical components from one another using thermal processes like distillation. These separative processes help make everything from fertilizer to plastics. But they are grossly inefficient. Via Separations has developed a new molecular filter using a graphene oxide scaffold and a unique manufacturing process to ensure a consistent pore size, no matter the size of the filter. And they've specifically designed it to be durable enough for chemical plants.

Impact
The company's passive filtration technology can reduce energy used in separative processes by 90%—or nearly the equivalent of all the energy used for gasoline-powered transportation in the US.

Zapata Computing

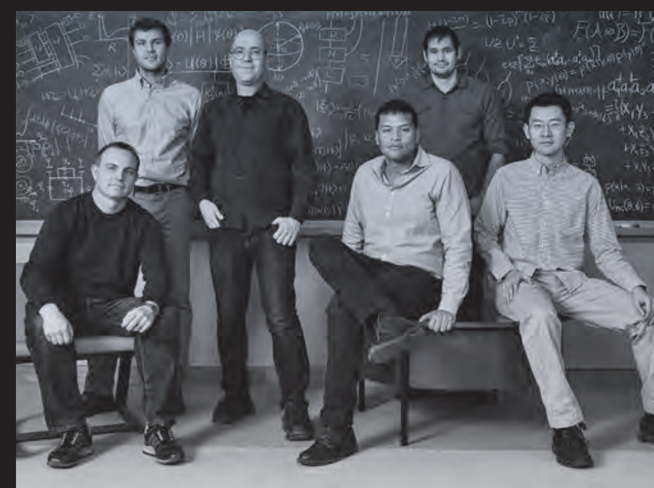
Founders
Chris Savoie, Alán Aspuru-Guzik, Peter Johnson, Jhonathan Romero Fontalvo, Jonathan Olson, Yudong Cao

Background
Aspuru-Guzik Research Group

Industry
Quantum Computing Software

Zapata Computing writes algorithms that harness the power of quantum computing to help predict and simulate some of the universe's most complex interactions, like how molecules behave at an atomic level. When used in tandem with quantum hardware, they have practical industrial applications, like predicting the structure and effect of new pharmaceutical drugs before they're synthesized in the lab, for example.

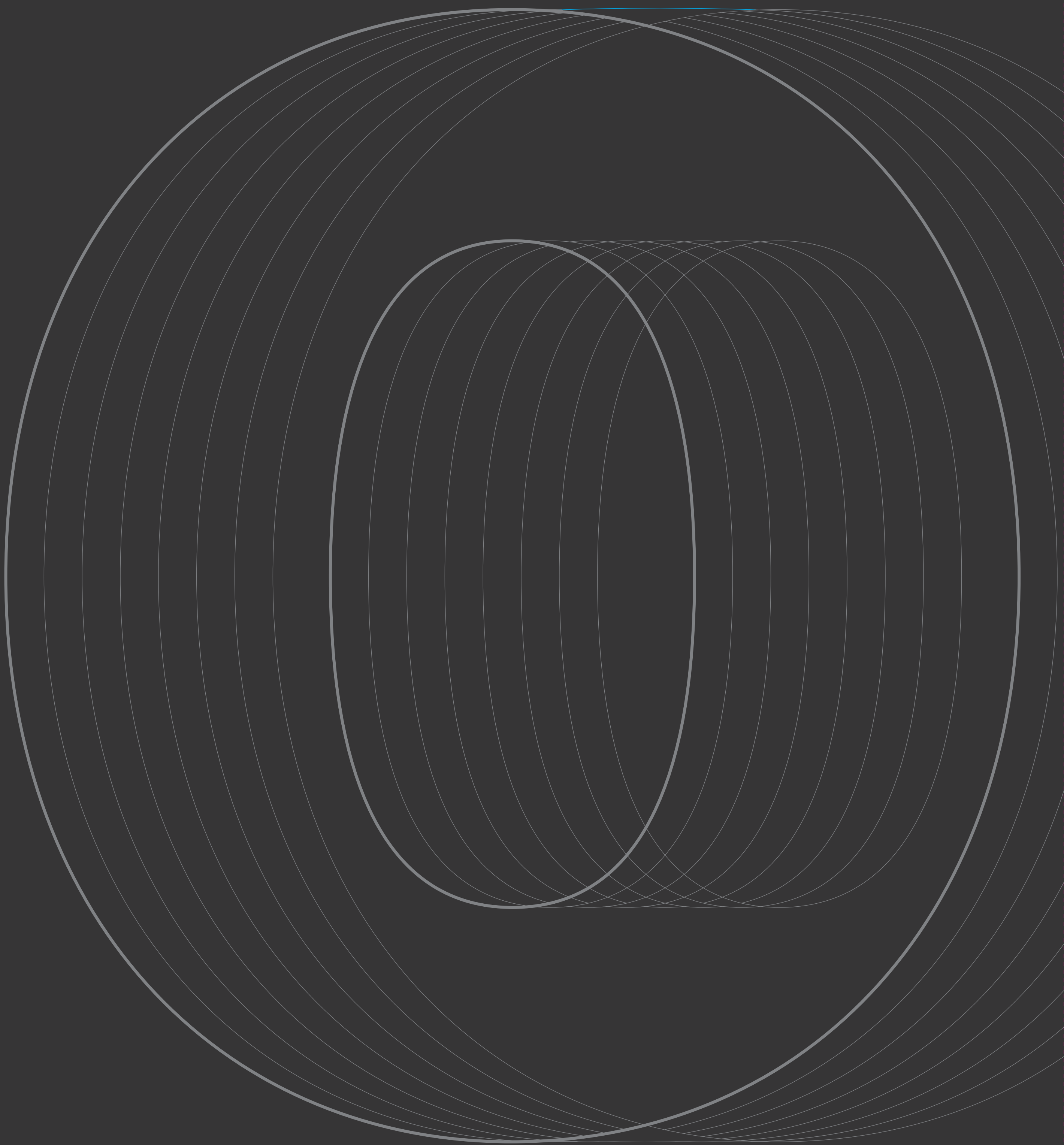
Impact
By creating algorithms that bridge advances in quantum computing hardware and commercial applications, Zapata has the potential of helping discover new life-saving molecules, energy efficient materials, and much more.



"Solving problems that are societally important, not just personally convenient." | "Bringing the best of the best together to innovate for a better world." | *"Societal impact rather than new toys and amusements."* | "The frontier technology that makes the unimaginable possible." | *"Technical challenges that could generate wealth while improving the lives of 10^6s-10^9s of people."* | "Solving hard problems the right way." | *"Tech that is grounded in deep science that is tough to commercialize due to significant technical risk."* | "It's what moves the needle." | *"It's harder, it can take longer, but the payoffs are higher."* | "Frontier science and breakthrough engineering tackling the world's biggest challenges." | *"Tough Tech is the backbone of any respectable industry."* | "Non trivial solutions to critical problems." | *"Problems too complex for academia and too hard for normal venture capital."* | "A Tough Tech company is a trailblazer, inventing new technologies that disrupts and transforms the status quo." | *"Tough Tech is faith in the power of curiosity."* | "Fundamental changes to human capabilities." | *"Non-trivial technology that has the power to change the way we as a species both live and interact with the world."*

THE ENGINE
Built by MIT

Tough Tech has a community, it has a stewardship, and it has a home - The Engine



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