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Sitting down with...Emily LeProust, CEO, Twist Bioscience

DNA synthesis company Twist Bioscience has developed a revolutionary, silicon-based approach to building synthetic DNA. By miniaturising chemistry, and maximising synthesis throughout, it has ramped up the availability and accessibility of synthetic DNA for the biotech and biopharma industries. Lu Rahman chatted with Twist co-founder and CEO **Emily LeProust** about its path to success.

LR: Can you give us a brief history of the company?

EL: Bill Banyai, Bill Peck (The Bills), and I founded Twist in 2013. The Bills invented a fantastic technology to write DNA using silicon, which had tremendous potential to scale output and decrease costs. We could develop and supply inexpensive molecular tools to advance synthetic biology, drug discovery, next-generation sequencing (NGS), and DNA data storage, to name a few.

At the time, synthetic DNA cost around 25 cents a base, which was expensive, and the process was relatively slow, which limited the applications. If a lab needed hundreds of genes, they would pay a lot for them, and they would have to wait a long time. It was a significant bottleneck we wanted to overcome.

Of course labs could clone their own genes, but to put it bluntly, cloning is a pain. At Twist, we often say, 'Friends don't let friends clone'; researchers had to spend all this time creating DNA before they could even run their experiments. It slowed productivity as researchers weren't spending their time collecting and observing new data underpinning important discoveries, instead they were stuck building things. So, the equation was quite simple. If we could produce more DNA and significantly decrease the costs, we could enable more research. We introduced DNA at 7-9 cents a base, and we can produce it in tremendous quantities. That economy means grant and investor money can go further, and labs can explore more with the same budget, ultimately pushing the envelope on what is possible. We had a successful Initial Public Offering (IPO) in 2018, and that helped fuel our growth.

LR: Describe Twist's silicon-based DNA synthesis platform.

EL: The chemistry needed to build DNA is well known; the Bills didn't invent that, but we have made some optimisations. Twist's key innovation was taking that chemistry, miniaturising it, and putting it on silicon. We manufacture the proprietary silicon surface in-house, reducing our costs, ensuring we could pass those savings down to the scientists using our tools.

In the same form factor as a plastic 96-well plate commonly found in labs, our proprietary DNA writers then make a million high-quality DNA oligos simultaneously, in a single day. These form the raw materials for the rest of our products. We find that the uniformity and quality of oligos manufactured in this way are exceptional. Starting with the highest quality raw materials affords us the flexibility to produce outstanding quality products.

In 2015, we launched our first product, Synthetic Genes. Today, we generate precisely synthesised Variant Libraries for antibody discovery, highly uniform target capture panels for NGS, Oligo Pools with oligos up to 300 bases,

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Antibodies against hard to drug targets, Cloned Genes, and Gene Fragments at industry leading prices and quality, and recently, positive RNA Controls for COVID-19 testing. We firmly believe that this is just the beginning, as when you produce raw materials at a lower cost and make a lot, people find creative ways to use them.

LR: In which fields does Twist's technology provide particular benefits?

EL: As DNA is a raw material and we service so many applications, it's hard to distill it down. At Twist, we really focus on seven main fields: microbiology, synthetic biology, oncology, precision medicine, drug discovery, sustainability and data storage. We also see our tools used heavily in the foundational research required to push these fields further.

A great example of how the quality of our products provides benefits is in targeted sequencing. Our custom and pre-designed sequencing panels effectively capture only the sequences researchers are interested in, removing 99% of the useless information from the experiment before it starts. Much deeper and more even coverage can then be achieved for each region of interest, giving researchers more precise data.

The high quality of the raw materials used to build each panel combined with our proprietary silicon-based technology leads to significantly increased capture efficiencies. Hard to sequence samples are suddenly accessible. For example, research hospitals and academic labs have been fixing thousands of biopsies in paraformaldehyde to reference in the future. This archiving process is extremely harsh on the DNA in the sample, often making it unreadable by standard NGS. With Twist's target capture probes, sequencing data with significant read depth can be extracted. This opens up a new world for understanding disease based on a wealth of data that can now be extracted from a previously untappable resource.

Another example is in drug discovery. In 2017, we launched Twist Biopharma, a division of Twist Bioscience focused on leveraging our DNA synthesis technology to rapidly discover high value antibodies. Our high volume output of quality oligos allows for the construction of precise synthetic antibody variant libraries. Instead of sifting through a single library of sequences to find hits, the team has built a "library of libraries." Each library is designed to focus on a specific hard to drug target – massively maximizing the success rate of discovering valuable hits while reducing the time-todiscovery. Partners are already leveraging this technology to identify new antibodies to treat disease.

Regarding sustainability, our world is currently dependent on gas and oil. Many of us have bought electric or hybrid cars to reduce our carbon footprint, but that does nothing about plastics or fertilizer, which are manufactured with oil.

Synthetic biology can engineer bacteria to deliver nitrogen directly to roots, which could mitigate the need for fertilizer. These tools can also be used to engineer plants that better resist disease, which has already been accomplished in bananas and papayas. We can also leverage synthetic biology to develop unique enzymes that degrade plastic for recycling and produce chemicals without generating so much waste.

Researchers use Twist's Synthetic Genes to build up the metabolism altering pathways in bacteria needed for these applications. Typically, this is an intensely manual process, where each gene requires validation that its orientation and its sequence is correct. We believe this process is a waste of time and potential, so we provide ready-cloned NGS verified genes to ensure that our customers will receive precisely the gene they designed without error. Instead of spending most of their time on pre-validation, our customers are out there collecting data. These rapid design-build-test cycles lead to an increased discovery rate for new solutions that help better our world.

One application I love is the production of spider silk, one of the strongest and lightest materials on Earth. Unfortunately, we can't farm spiders because they eat each other. On the other hand, with synthetic biology, using microbes to generate the proteins that constitute spider silk, we could scale spider silk production. This material has incredible potential and could eventually replacecarbon composites in cars, planes, construction materials, etc. It's good for the Earth and great for spiders.

LR: How important is collaboration for Twist? How have you worked collaboratively with customers?

EL: Collaboration is beyond essential for Twist. We make synthetic biology tools and products that can help drive research and development. If we made concrete, we might make the best concrete in the world, but it would mean nothing if we didn't partner with construction companies.

The organisations we work with utilise our synthetic DNA products to do meaningful work. We have partnered with researchers at the Vanderbilt Vaccine Center for several years. Last year, they led a DARPA sprint to develop therapeutic antibodies against a fictional pathogen.

Unfortunately, that scenario became all too real when SARS-CoV-2 hit in early 2020. We have continued working with Vanderbilt and others to develop neutralizing antibodies to treat COVID-19.

A lot of what we do helps companies create more efficient processes. Last year, we worked with Arzeda, TeselaGen Biotechnology, and Labcyte to develop a DNA assembly platform to encode Arzeda's designed proteins, accelerating the process and reducing costs.

I am especially excited about two recent collaborations: Twist Biopharma and Takeda, and Twist Biopharma and Neogene Therapeutics. Takeda is leveraging our Library of Libraries. Combined with Takeda's deep history in drug discovery, this partnership sets an exciting path to novel antibody therapeutic development. For Neogene, Twist Biopharma is developing a novel T Cell Receptor library, enabling Neogene to expedite the identification and genetic engineering of TCR genes to create personalised T cell therapies for cancer.

LR: You have a vision for science and technology and how it can create meaningful solutions. How does this play out within the company in terms of nurturing talent and innovation and sharing with customers?

EL: We stand by our slogan, 'Diversity is in our DNA'. Twist has a diverse workforce, and that is one of the reasons for our success. We are focused on recruiting the most talented people. Once you remove all of the artificial restrictions around gender, sexual orientation, race, and everything else, it opens the field in a marvellous way.

While we have been working hard to develop technologies, we've also been building a safe and welcoming environment where we respect who people are and the ideas they can bring to the table, and that opens the door to profound creativity. Whether they are a bench scientist, an artist, or an executive, each person at Twist simply has to embody our four guiding principles: grit, impact, service, and trust.

To me, gathering people from diverse backgrounds with different talents, life experiences, and points of view creates this beautiful stew of ideas. It's kind of magical.

LR: How do you feel your business interacts with the wider US biotech space? Do you have any sense of where the main areas of opportunity will be in the US biotech field in the next five-10 years?

EL: Circling back to my concrete analogy, it doesn't matter what kind of buildings and architecture come in and out of vogue. For the most part, companies still need the same raw materials. In a similar vein, synthetic DNA is largely application-agnostic.

I'm sure that, in some respects, synthetic DNA applications will remain mostly similar to the ones I've described. However, I also believe labs will develop novel ways to use DNA to explore biology, sustainability, and other realms.

Our role is to produce high-quality synthetic DNA at greater scales and reduce the cost per base. If we continue to do this, we will continue to add value for our customers, allowing them to accelerate their research. We will be ready to adapt as needed. You can take our new products in infectious diseases catapulted by the COVID-19 pandemic as a specific example of our ability to innovate and execute.

On an industry level, synthetic biology will always be an essential part of the biomedical research continuum, and that will expand.

But what intrigues me the most is sustainability. In my view, synthetic biology can help us maintain our lifestyles but do it better. That means less carbon in the atmosphere, fewer chemicals and plastics in the ground, rivers, and oceans. We get to keep what we have but do it in a much cleaner, more balanced environment.

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LR: You were recently honoured with the BIO Rosalind Franklin Award for your work in the biobased economy and biotech innovation. In the bigger picture, you are considered a pioneer in high-throughput DNA synthesis and sequencing. What are the significance of these accolades and how do they fit in with Twist's business?

EL: It's only recently that Rosalind Franklin started receiving due credit for her tremendous contributions to Watson and Crick's Nobel prize-winning work on DNA structure. I am privileged to live in a different time, in which my contributions are more likely to be recognised. I owe so much to Franklin and many others. They endured a lot so that we at Twist could thrive.

In whatever form they come, honours are always welcome, but science is a team sport, and I've had a lot of help along the way. What matters at the end of the day is the work that we do. When 'The Bills' and I founded Twist, we weren't looking for honours. We were frustrated that synthetic DNA was so expensive and so hard to obtain.

Many good ideas had to be tabled because labs just didn't have the resources in time or money or both to move forward. I believe Twist has helped change those economics, successfully democratising access to DNA and other molecular tools, and that makes me quite happy.

Still, there's a lot more that needs to be done, and I never want to lose the startup mentality that has driven us forward. I am always grateful for any accolades that come to Twist or me, and at the same time, I know we can do even more to improve health and sustainability.

BIOGRAPHY

As an early pioneer in the high-throughput synthesis and sequencing of DNA, Dr. LeProust is disrupting the process of gene synthesis to enable the exponential growth of synthetic biology applications in multiple fields including medicine, DNA data storage, agricultural biology, and industrial chemicals. In 2015, she was named one of Foreign Policy's 100 Leading Global Thinkers for fast-tracking the building blocks of life, and Fast Company named her one of the most creative people in business for synthesising DNA faster than ever. Prior to Twist Bioscience, she worked at Agilent Technologies and at the University of Houston developing DNA and RNA parallel synthesis processes on solid support, a project developed commercially by Xeotron Corporation. Dr. LeProust has published over 30 peer-reviewed papers—many on applications of synthetic DNA, and is the author of numerous patents. She earned her Ph.D. in organic chemistry from the University of Houston and her M.Sc. in industrial chemistry from the Lyon School of Industrial Chemistry in France.

To learn more, please visit Twist Bioscience.

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