Ag giant enters vertical farming

German agbiotech giant Bayer and Singapore's sovereign fund Temasek have launched a company to develop and sell new vegetable seed varieties tailored to vertical farms. The startup, called **Unfold** and unveiled in August, will license rights to seed germplasm from Bayer's vegetable portfolio, especially varieties of crops such as lettuce, spinach, tomatoes, pepper and cucumbers, which are particularly well suited to indoor growing environments. The company is building an R&D facility in Davis, California to carry out the work. "Unfold will combine leading seed genetics with the best agtech experts in order to dramatically advance productivity, flavour and other consumer preferences," said Unfold CEO John Purcell in a statement. The company seeks to leverage its intellectual property in seeds and digital solutions to galvanize the potential of vertical farming to connect with the retail industry and directly with consumers.

Vertical farms can function with artificial light, in reduced spaces or disused buildings, and overall consume less water. This makes them particularly well suited to urban settings or harsh climates, and a reduced environmental footprint aligns them with the **Sustainable Development Goals** set by the United Nations for 2030. The COVID-19 pandemic has also raised awareness of how disruptions in logistics and transportation can rapidly endanger food security. These are challenges that vertical farms, with their fresh local produce and shortened supply chain could help overcome. Unfold is a collaboration between Leaps by Bayer (Bayer AG's investment arm) and Temasek, a global investment company, and raised \$30 million in an initial funding round. The market size for vertical farming was \$2.1 billion in 2018 and is forecasted to reach \$12 billion by 2026, according to a **report** by Fortune Business Insights. Bayer is the company that in 2018 acquired GMO crop producer Monsanto, but the new entity will not develop genetically modified seed varieties but instead pursue other breeding techniques, such as gene editing.

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California. They recognized the difficulty of coaxing TdT to accept modified nucleotides, so instead **modified the enzyme itself** — tethering each TdT molecule to an individual deoxyribonucleoside triphosphate molecule with a reversible linker. "When you expose the 3' end of the nascent strand to that conjugate, it adds the nucleotide, and then the whole enzyme remains attached to the 3' end," explains Arlow. "That blocks other conjugate molecules from adding a second base." This strategy requires more enzyme, but Arlow notes that it remains cost-effective because it eliminates the need for high concentrations of expensive modified nucleotides.

Chemical modification is not strictly essential for TdT-based synthesis, however. Henry Lee devised a modification-free strategy with his colleagues while working as a postdoc in George Church's lab at Harvard University. The approach essentially **stages a competition between two enzymes**: the TdT that adds nucleotides to the DNA strand and an apyrase enzyme that chemically inactivates the remaining nucleotides so that they can no longer be added by TdT. This is not as precise as the terminator-based strategies, making it less ideal for synthetic biology applications that require extremely accurate construction of a desired sequence, but represents a good DNA storage solution. "You get a net addition, with some distribution in the number of bases that is added," says Lee. He sees this approach as a good match for DNA-based data storage schemes, which rely heavily on redundancy and error-correction mechanisms, and this application is a focus of his startup, Kern Systems.

But as suited as TdT is to enzymatic synthesis, several important limitations have manifested as more companies have begun to test its capabilities. For example, Lee notes that the enzyme exhibits some notable biases. "It cares about the terminal sequence that it is bound to, and it cares about the incoming nucleotide," he says. This could in turn affect the reliability of the process and the efficiency with which certain sequences can be produced. Performance can also decline if the strand being synthesized begins to form secondary structures.

More protein engineering may therefore be necessary to improve the enzyme's performance and bolster its reliability. It was this need that prompted Molecular Assemblies' decision to partner with Codexis. "We've had a protein-engineering effort in the company since we opened our doors," says Efcavitch, "but Codexis has a very high-throughput protein evolution process in place and a long track record, and it was a simple make-versus-buy decision."

TdT is also not the only enzyme available for this purpose, even if it is the best known. For example, Camena Bioscience is using a proprietary combination of enzymes to achieve template-free DNA synthesis from trinucleotide building blocks. "Through a number of tricks, we've been able to really bolster the accuracy of synthesis," says CEO and cofounder Steve Harvey.

"We spent years building DNA constructs and pathways [with chemical synthesis], and it was very frustrating and painful work," says Gariel. "You start thinking, 'Why am I wasting my youth doing this stuff?'"

After years of effort, these forays into enzymatic synthesis are now reaching some important milestones in terms of performance. DNA Script has managed to achieve up to 99.7% coupling efficiency with its enzymatic process — a measure of the proportion of strands that successfully incorporate the desired nucleotide at each step. This exceeds the estimated 99.2–99.3% efficiency of phosphoramidite chemistry, says Gariel, and his company reported successful synthesis of a **280-base sequence** in February. Camena is operating in a similar range with its technology, which can now routinely **produce 300-mers** with greater than 99.9% coupling efficiency according to Harvey. But longer sequences remain challenging, and for now, many enzymatic synthesis companies have prioritized boosting reliability and speed, relying on higher-level assembly processes rather than pushing the length limits farther.

With at least half a dozen companies now active in the space (Table 1), a variety of business models have emerged. Nuclera and DNA Script are both working on benchtop DNA printer instruments. DNA Script is closest to commercialization, having developed a prototype of its Syntax benchtop instrument. Syntax is roughly the size of an Illumina HiSeq sequencer and is slated to enter beta testing before the end of 2020. "We designed the first cartridges to be able to make a 96-well plate of 60-mers within six to seven hours," says Gariel, noting that the resulting oligos are also purified and subjected to quality control within the instrument, enabling immediate use. Huang reports that Nuclera's instrument is now in the final stages of development and could be ready for a demo in early 2021 and launch by early 2022.