5 Biotech trends I'm excited about in 2020

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It’s become a recent tradition for me to start the year with some prognostications about what’s on the horizon for biotechnology. Last year, I talked about in vitro physiology models, the wonderful world of non-Cas9 nucleases, exotic microbial production hosts, and the increasingly blurring line between the biological and the inorganic. I was thrilled to see how strongly the post resonated with our readers, I and couldn't pass up the opportunity to discuss what we have to look forward to in 2020.

1. Engineered resource utilization in biosynthesis

Classically, metabolic engineering research has put a premium on expanding the product range of engineered organisms, perhaps by managing metabolic flux or introducing exogenous synthetic pathways. The idea here is to start with a microorganism that's genetically tractable and easy to feed and then modify it to produce compounds of interest in energy, health, commercial, or industrial contexts. Ideal organisms are phototrophic, meaning they contain the photosynthetic machinery to use light energy to perform chemical reactions, or they consume glucose or related sugars, which are abundantly available as cheap commodities.

Comparatively less work has been put into engineering biosynthetic organisms to use unusual sources of carbon and energy. But increasing carbon dioxide emissions have prompted a new way of thinking about resource utilization in production strains: a microorganism that can assimilate CO2, or a chemical derivative of CO2 like methanol, suddenly has an increasing supply of easily accessible substrate and simultaneously may play a small part in remediating atmospheric carbon dioxide. As additional resource utilization pathways are engineered, it may become possible to produce specialty chemicals from whatever bulk chemical happens to be on hand rather than requiring strain-specific growth media.

2. CRISPR/Cas technology beyond genome editing

It wouldn't be Trends in Biotechnology without novel applications of CRISPR. The capacity of CRISPR/Cas tools to edit genomes barely needs an introduction at this point, and last year I talked about how the expanding array of CRISPR proteins beyond the most commonly used Cas9 will eventually be useful for application-specific genome editing approaches. (There still haven’t been many gene-editing applications of Cas14, but I'm sure they're coming.)

In parallel, uses of CRISPR/Cas systems are being devised beyond their "traditional" application of editing genomes. Instead inserting or deleting entire regions of a gene, base editing alters single nucleobases (for

example, C to T), and the even newer prime editing is a search-and-replace method to write new DNA on-site without requiring a guide nucleic acid. CRISPRi and CRISPRa inhibit and activate gene expression, which can be used to conduct genetic screens. And an even further removed technological approach is to use CRISPR/Cas systems as biosensors, for instance to identify the presence of a pathogen's DNA for diagnostic purposes.

All of these novel applications exploit the ability of Cas proteins to recognize DNA or RNA but intentionally impair their nucleic-acid breaking function. Then, new functionality is added by engineering the protein with, for example, deaminase or signal transduction activity. In principle, virtually any protein function may be able to be added to Cas, meaning that a whole host of enzymatic activity will likely be coupled to CRISPR systems in the coming years.

3. Synthetic genomes and cells

A North Star ambition of synthetic biology is to create lifelike, self-sustaining cellular systems with bespoke genomes, precisely tailored to specific functions. Like genome-editing technology, this is interesting in the biotechnology context both as a platform—an engineered system rooted in biology with its own design language and methods development—and for practical implementations, as an artisanal biocatalyst, an on-demand in situ source of therapeutic proteins, or a selective surveillance agent that can detect pathogens and contaminants in a food or water supply.

This emerging technology sounds the closest thing to science fiction out of any of the trends on this list, and I'm certainly not predicting that you'll be able to go to your favorite scientific supply company and order up a synthetic microorganism this year or next. But there has been considerable progress toward that possibility over the past decade, with the design of artificial bacterial and yeast genomes, and more recently the idea of recoding genomes to use less than the standard set of 64 codons. Concurrent efforts have studied how to create artificial cells out of a minimal set of biochemical components like cytoskeletal structures and nested compartments. A key next step will be to better integrate "bottom up" efforts to synthesize cellular components from scratch with the "top down" work of minimizing existing genomes to retain only desired functions.

4. Cell-free biosynthesis

Alternatively to designing a whole cell to do what you want it to (not currently feasible) or starting from an existing cell and forcing it to do something it doesn't want to (possible, but often laborious and low-yielding), another emerging approach to biosynthesis is to remove as much of the biology as possible. Cell-free techniques reproduce the necessary parts of cellular metabolism—energy sources, enzymes, and

cofactors—outside of cells, eliminating the competing priorities of cellular growth and maintenance, obviating the need for transport proteins or efflux pathways, and allowing the synthesis of toxic compounds.

Cell-free synthesis has been possible for several years but has so far focused primarily on relatively simple molecules, like producing fuel compounds or fixing carbon dioxide. As metabolic engineering moves toward tackling more complex molecules like natural products, the ability to synthesize natural products such as cannabinoids outside of cells has advanced too. The many classes of natural products combined with this recent success suggest that this will be an active area of research sooner rather than later.

5. Therapeutic biomanufacturing

The production of therapeutic proteins and even cells is nothing new, but the recent energy in this field is turning lab-scale production platforms into practically useful strategies for treating disease. One approach is to install platforms right at the point of medical need, which has the advantage of being able to synthesize protein drugs on demand; the drawback is a much bigger regulatory challenge than onsite small molecule production because of the complexities of understanding the activity of biosimilar therapeutics. The other approach is to create a consensus among scientists, engineers, manufacturers, regulators, and distributors—to name just a few stakeholders—to define best practices and common quality control parameters toward the goal of scaling up a fussy, unpredictable biosynthetic scheme into a large-scale industrial protocol. Given the rapid advance in the basic science underlying CAR T cells, induced pluripotent stem cells, exosomes, and other biologics at the organelle or cell scale, continued standardization efforts will be critical to translate these technologies to patient therapies.After waiting in eager anticipation for a decision on their paper, when authors receive a rejection letter from this journal, it can be frustrating and confusing, sending these letters is not favorite part of the job. Though our editors need to be selective about the papers they choose to publish, they also want to help every author to find the perfect home for their manuscript.

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