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PRODUCT AND HOST ENGINEERING FOR LOW-COST MANUFACTURING OF THERAPEUTIC PROTEINS IN YEAST

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The COVID-19 pandemic revealed a global need for affordable, accessible biologic medicines such as prophylactic vaccines and antiviral monoclonal antibodies. Indeed, two years after the emergence of SARS-CoV-2, access to vaccines and therapeutic proteins is still limited in low- and middle-income countries. Long development timelines, expensive manufacturing requirements, and stringent storage conditions all contribute to the high cost of biologic medicines generally. While therapeutic proteins may have higher stability and less stringent storage requirements than newer modalities like therapeutic RNAs, complex therapeutic proteins like antibodies are typically produced in mammalian cells, which increase costs due to sterility requirements, expensive feedstocks, and long cell line development timelines. Additionally, there is limited total global capacity for manufacturing therapeutic protein in mammalian hosts.

Alternative hosts have potential to increase the accessibility of therapeutic proteins by shortening development timelines, lowering manufacturing costs, and increasing the global manufacturing capacity. Single-celled eukaryotes such as yeasts represent a “sweet spot” for protein manufacturing—yeasts grow to high cell densities on inexpensive feedstocks like bacteria, and can secrete products into the extracellular space like mammalian cells. One yeast, Komagataella phaffii (Pichia pastoris), is currently used for manufacturing of insulin and subunit vaccines in LMICs, and has recently been approved by the FDA for the manufacture of several complex therapeutic proteins, including a monoclonal antibody. Wider adoption of alternative hosts such as K. phaffii in has been hampered by bespoke manufacturing challenges for unique therapeutic proteins such as subunit vaccines, and low upstream titers of complex therapeutic proteins with stringent quality requirements such as monoclonal antibodies.

In this talk, I will discuss engineering efforts to enable and improve the manufacturing of several therapeutic proteins in K. phaffii. First, we improved the manufacturing of a trivalent subunit protein vaccine for rotavirus by host-informed product sequence engineering. Recently, we applied both product engineering and host strain engineering to rapidly develop a subunit vaccine for COVID-19 that can be manufactured at low-cost and at large scale. I will describe the design of the product, efforts that informed manufacturing scale up, and preclinical testing of the vaccine product. This product is now manufactured at the Serum Institute of India, and is currently in clinical trials. Finally, I will discuss how these engineering strategies can be applied to other needed therapeutics like monoclonal antibodies.