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Designing a microbial cultivation platform for continuous biopharmaceutical production

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DESIGNING A MICROBIAL CULTIVATION PLATFORM FOR CONTINUOUS BIOPHARMACEUTICAL PRODUCTION

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The existing biopharmaceutical manufacturing paradigm is poorly suited to produce biologic drugs on demand at a point-of-care. Generally, commercial-scale (~2,000 - 10,000 L) manufacturing using fed-batch cultivation and fixed stainless-steel infrastructure is concentrated in developed nations and results in process cycle times on the order of weeks to months.[1,2] Coupled with the complex logistical challenges associated with continuous "plant-to-patient" cold-chains, the geographically biased nature of therapeutic protein production today can limit access to biologic drugs in developing areas of the world.[3] There is an opportunity to create technologies capable of rapidly generating biopharmaceuticals *in situ* in emergency situations, in remote healthcare settings, and in the battlefield. A platform that incorporates a modular suite of bioreactor, purification, and in-line analytics technologies has the potential to bridge this gap if developed in parallel with appropriately engineered stains of a flexible expression host. This poster will describe a multifaceted approach towards the development of a fully automated bench-scale perfusion process for the cultivation of *Pichia pastoris* and expression of therapeutically relevant heterologous proteins. We demonstrate the application of computational fluid dynamics (CFD) simulations to the optimization of the cultivation environment within our bench-top bioreactors. We further show that *Pichia pastoris* is amenable to secreting a variety of recombinant proteins spanning a range of preexisting drug classes (*e.g.* hormones, cytokines, monoclonal antibodies, vaccine antigens). Among these therapeutic proteins are molecules that require proper co-/post-translational processing for bioactivity. We envision that the development of *P. pastoris* strains with the capability to perform these critical processing steps *in vivo* will mitigate the need to chemically modify proteins post-expression and reduce the number of unit operations required in a typical upstream process.

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