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## **ROBUST PROTEIN PRODUCTION AND SECRETION IN BACTERIA USING THE TYPE III SECRETION SYSTEM**

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Protein production is a multi-billion dollar industry, with applications in pharmaceuticals, industrial enzyme use (eg in laundry detergent), and biomaterials. Bacteria are receiving renewed interest as protein production hosts because of their fast growth and tractability. The *Salmonella enterica* Type III Secretion System secretes non-native proteins at product titers of up to 400 mg/L in rich media, but is highly sensitive to environmental and growth conditions and therefore not robust. This system is nonetheless an ideal process for protein production applications because it is non-essential for bacterial metabolism and allows for target proteins to cross both bacterial membranes in one step, via characteristic needle-like protein structures. We engineered an optimized, more robust secreting strain of Salmonella for the high-titer production of a variety of biochemically challenging heterologous proteins, such as growth factors, antibodies, and toxic antimicrobial peptides. To do so required manipulating regulation, engineering the protein components of the apparatus, and optimizing media composition and growth parameters. Now that the system is producing protein at commercially-relevant titers and quality, we also established a set of assays to test the safety of the new strain, toward an effort to create a version of the secreting microbe that is “generally recognized as safe” (GRAS).