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Gram positive cell factories: production of disulfide-rich recombinant Plasmodium falciparum malaria vaccine candidates in Lactococcus lactis

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The production of recombinant proteins with proper conformation, appropriate post-translational modifications in an easily scalable and cost-effective system is challenging. *Lactococcus lactis* has recently been identified as an efficient Gram positive cell factory for the production of recombinant protein. We and others have used this expression host for the production of selected malaria vaccine candidates. The safety of this production system has been confirmed in multiple clinical trials. Here we have explored *L. lactis* cell factories for the production of around 50 representative *Plasmodium falciparum* antigens from different stages (Pre-erythrocyte, asexual and sexual) with varying sizes (ranging from 9-90 kDa) and varying degree of predicted structural complexities including thirty antigens with multiple predicted structural disulfide bonds, those which are considered difficult-to-produce proteins. Of the 50 recombinant constructs attempted in the *L. lactis* expression system, the initial expression efficiency was 60% with 30 out of 50 recombinant gene constructs producing high levels of secreted recombinant protein. The majority of the constructs which failed to produce a recombinant protein were found to consist of multiple intra-molecular disulfide-bonds. We found that these disulfide-rich constructs could be produced in high yields when genetically fused to an intrinsically disorder protein domain (GLURP-R0). By exploiting the distinct biophysical and structural properties of the intrinsically disordered protein region we developed a simple heat-based strategy for fast purification of the disulfide-rich protein domains in yields ranging from 1 to 40 mg /L. Conclusions: A novel procedure for the production and purification of disulfide-rich recombinant proteins in *L. lactis* is described.

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