6-12-2022

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Luigi Sollai

Angela Daniele

Giulia Iannello

Federico Pippi

Antonia De Felice

See next page for additional authors

Authors

Luigi Sollai, Angela Daniele, Giulia Iannello, Federico Pippi, Antonia De Felice, Francesca Necchi, Rocio Cannals, Francesco Berlanda Scorza, and Anna Maria Colucci

INTENSIFIED HIGH YIELD PRODUCTION OF GMMA BASED VACCINES FOR HIGH BURDEN NEGLECTED DISEASE

Luigi Sollai, GSK-GVGH, Italy
luigi.x.sollai@gsk.com
Angela Daniele, GSK-GVGH, Italy
Giulia Iannello, GSK-GVGH, Italy
Federico Pippi, GSK-GVGH, Italy
Antonia De Felice, GSK-GVGH, Italy
Francesca Necchi, GSK-GVGH, Italy
Rocio Canals, GSK-GVGH, Italy
Francesco Berlanda Scorza, GSK-GVGH, Italy
Anna Maria Colucci, GSK-GVGH, Italy

Key Words: intensified process, continuous flow fermentation, continuous manufacturing, disposable bioreactor.

Vaccines are among the most important public health interventions currently available. The global demand for vaccines is growing due to global population growth, ongoing global immunization campaigns and the increase of antibiotic-resistant bacteria. Vaccines are of high importance in Low- and Middle-Income Countries (LMIC) where millions of deaths occur annually due to vaccines-preventable diseases. Global coverage would need at least 200 million doses annually of a two-dose vaccine to cover the at-risk birth cohort, and considerably more for catch up vaccination during a roll out phase. Especially for vaccines against diseases in LMIC, there is a major added constraint: the vaccine production cost per unit and manufacturing facilities investments must be minimized to ensure the vaccines will be both viable and sustainable.

For diseases caused by Gram-negative bacteria, the vaccine platform based on the GMMA technology is promising. GMMA are highly immunogenic outer membrane exosomes produced from genetically engineered bacteria modified for high yield hyper-blebbing that can be purified with minimal downstream processing. Simple robust scalable processes make GMMA ideal for cost-conscious vaccines.

GSK Vaccines Institute for Global Health (GVGH) is developing several GMMA-based vaccines. Specifically, a GMMA-based bivalent *Salmonella* vaccine against invasive non-typhoidal salmonellosis (iNTS), a high burden disease causing a major public health problem in sub-Saharan Africa, and a combination with a WHO pre-qualified Typhoid Conjugate Vaccine (TCV) from Biological E, iNTS-TCV vaccine, are under development by GVGH.

We demonstrate how GMMA platform is suitable for intensified manufacturing and industrial manufacturing with increased flexibility on the bioreactor to be used, single-use vs stainless-steel bioreactor, enhancing the process transferability. Over 28 hours of continuous fermentation from a small-scale (3 L) bioreactor, it was obtained the equivalent quantity of GMMA that was produced in a pilot scale (30 L) fermentation run in batch mode. This dramatically reduces the required footprint of the fermentation system, manufacturing suite and investment costs.

Moreover, GVGH tested in addition the GMMA manufacturing production in disposable bioreactor, producing GMP grade material comparable to the drug substance produced in standard stainless-steel bioreactor. Both intensified manufacturing and single-use bioreactors are indeed an attractive option especially for LMIC GMP facilities. Their implementation might result in reducing investment, limiting operational costs, accelerating clinical manufacturing and reducing time to licensure, vital and of utmost importance especially for Global Health vaccines pipeline.