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Development of the full length single chain gp120-CD4 (FLSC), a novel vaccine for HIV prevention

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Obtaining a practical, efficacious vaccine against HIV has been a public health priority for over 30 years. We have developed the Full-length Single Chain (FLSC) in order to induce broader immunity, including against new conserved epitopes, compared to conventional gp120 or trimeric gp140s. The FLSC vaccine is fusion protein consisting of a modified full length gp120 protein, derived from HIVBaL and the first two domains (D1D2) of human CD4, genetically fused via a 20 amino acid linker. Immunization with FLSC was able to protect rhesus macaques against rectal challenge of heterologous neutralization resistant SHIV(162P3) and SIVmac251. Efficacy tracked with Fc-mediated effector function of the antibody provided that the concurrent anti-vaccine T cell response is minimal. Protection is lost over time as requisite antibody titers declined consistent with the evanescent quality of anti-envelope humoral responses. To advance the FLSC into clinical trials, a master cell bank expressing human FLSC was prepared from G293H, a derivative of HEK-293 cell that grows in suspension, using the GPEx® retrovector transduction system. Bioreactor production rates were consistent from the 2L to the 200L scale, yielding approximately 1 gms/liter after downstream purification. Drug substance was predominately monomeric and expressed the expected CD4 induced structure. Potency studies with the Alum formulated drug product demonstrated a significant relationship between the dose of the FLSC/Alum (IHV01) and the induction of the desired CD4i directed immune response. Immunogenicity studies performed in rhesus macaques showed that the FLSC/Alum formulation induced antibodies directed to CD4i epitopes and mediated ADCC activity while T-cell responses were modest. Toxicity studies performed in rabbits and cynomolgus macaques demonstrated that the vaccine was safe and did not induce any deleterious autoimmune effects directed to CD4. A dose escalation phase 1 clinical trial with IHV01 has started at the Institute for Human Virology in Baltimore, MD.

Biography

Timothy R Fouts is one of the Founders and Principle Scientists at Profectus Biosciences. He directs a team of scientists in the discovery and preclinical development of vaccines, small molecule and antibody based antiviral therapies and microbicides that are within the Profectus research portfolio in particular HIV and certain biothreat viruses. He has more than 35 scientific publications that have appeared in peer-reviewed journals and book chapters. He has received his PhD in Immunology from the University of Maryland, Baltimore and did a Postdoctoral Fellowship at the Aaron Diamond AIDS Research Center at Rockefeller University in NYC.

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