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### **Adjuvant-Free Potentiation of Vaccines by Red Blood Cell Targeting In Vivo**

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We are developing a strategy for augmenting the potency of immunogens without the need for immune adjuvants. It is based on the use of an immunotargeted streptavidin fusion protein to which any biotinylated immunogen can be coupled prior to administration. The fusion protein, expressed in bacteria, is species specific. The fusion protein targeting murine RBC (FP4mu) is comprised of (1) a single chain fragment derived from a monoclonal antibody that recognizes a surface protein on murine erythrocytes, and (2) streptavidin. The immunogen, once coupled to FP4mu and injected, homes to the erythrocyte surface whence it is transported to the reticuloendothelial system and presented efficiently to the immune system. Model immunization studies in mice have been conducted with several immunogens, including the flu peptide M2e, which represents the 23 amino acid ectodomain of influenza virus M2 protein. These studies have shown an absolute increase in antibody titer and a substantial dose-sparing effect by coupling the antigen to FP4mu. The combination of these two effects results in up to 4 orders of magnitude of increased immunogenic potency for this weak antigen, without the use of exogenous adjuvants. Immunization and repeated boosting with FP4mu tracked for 7 weeks is safe in mice, which exhibit normal weight gain, differential blood counts and histology and the absence of detectable anti-RBC autoantibodies. Anti-peptide antibodies from immunized mice predominate in IgG1, but substantial titers of IgG2a, IgG2b and IgG3 are also present. This effective strategy for enhancing immunogenicity without adjuvants and with a convenient avidin-biotin coupling mechanism is being adapted to other animal species and to humans by the construction of analogous fusion proteins.