Neutralization of sFasL Directly Blocks Acantholysis without Immunosuppression: PC111, a monoclonal anti-Fas ligand (CD95L) antibody for pemphigus

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Pemphigus is a rare and debilitating autoimmune blistering disease due to keratinocyte apoptosis and to cell-cell detachment (acantholysis). Treatments for pemphigus focus on a broad control of the immune system using classical therapies, such as corticosteroids, or newer drugs, like rituximab that regulate B-cell development. Because these immunosuppressive medicines may be associated with severe side effects, gradual onset of action and clinical relapse, new and more targeted therapies are needed to provide rapid, safe and complete responses. Our mechanistic studies into the molecular pathology of pemphigus have revealed a critical role for soluble Fas ligand (sFasL) in driving keratinocyte apoptosis and acantholysis *in vitro* and *in vivo* following addition of pemphigus patient autoantibodies (Lotti *et al*., 2018). Critically, use of a mouse reactive surrogate antibody against FasL is efficacious in both acute and chronic models of pemphigus. Our initial development candidate, PC111, is a fully human IgG4 with high affinity to Fas ligand (K_D=150 pM) and potent activity in human keratinocyte apoptosis/acantholysis assays (IC50 < 0.1 nM). Preliminary biophysical characterization shows high protein expression and purification from HEK or CHO lines with minor aggregation only under extreme acid conditions. PC111 was effectively concentrated to >70 mg/mL (precipitation concentration not yet attained) supporting development of a subcutaneous formulation. In-silico analysis with EpiMatrix Tregitope software (score = -31) suggests a low risk for immunogenicity. IND/CTA enabling CMC, PK, toxicology and translational studies are initiating so that we may evaluate this novel and differentiated therapeutic mechanism in the clinic.

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