PC111, a monoclonal anti-Fas Ligand antibody, blocks blister formation in human pemphigus

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The disease: PEMPHIGUS

HIGH UNMET MEDICAL NEED
- Chronic, debilitating and life-threatening condition
- Diagnosed in middle aged persons
- Treated with generalized immunosuppressants (severe side effects, relapses) (Murrell et al, 2019)
- Mortality rate 5-15% due to treatment side effects, estimated to be 3.3 times higher than among age- and sex-matched controls.

ROLE OF SOLUBLE FASL IN PEMPHIGUS

- Pemphigus autoantibodies (PVIgG) trigger the release of FasL from keratinocytes (Wang et al, 2004) (A) and the high levels of FasL in patients’ sera (Puviani et al, 2003) (B)
- Moreover caspase-3 (in red) is not activated in siFasL keratinocytes upon PVIgG treatment (C) (Lotti et al, 2018).
- Soluble FasL is essential for the process of blister formation in pemphigus. Indeed, animals KO for the sFasL (siFasL) are protected from PVIgG-induced acantholysis, unlike WT mice and animals that are KO for membrane FasL (mFasL) (Lotti et al, 2018).

WORKING HYPOTHESIS

- FasL, released from keratinocytes upon PVIgG binding, induces desmoglein cleavage and activation of caspases.

AIM: TO DEVELOP A NEW MONOCLONAL AB TO TARGET THE FAS/FASL SYSTEM IN PEMPHIGUS
- Maintain complete remission
- Steroid sparing or steroid avoiding
- Safe for chronic administration
- Avoiding long term immunosuppression

RESULTS

PRELIMINARY RESULTS

In vivo

1) Anti-murine FasL antibody prevents blister formation (A) and apoptosis activation (B, C) in the passive transfer pemphigus mouse model

2) Anti-murine FasL antibody treatment is efficacious in an adult active pemphigus mouse model, with a rapid onset of the effect and no sign of acute toxicity

THE PRODUCT: PC111

- Fully human IgG4
- High affinity to human soluble Fas ligand (KD=150 pM), by BIACORE analysis
- Preliminary biological 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.

PC111 EFFICACY IN PEMPHIGUS

in vitro

PC111 inhibits sFasL-mediated acantholysis induced by PVIgG treatment with an IC50 of 0.0097 µg/mL (nM concentration)

PC111 EFFICACY IN PEMPHIGUS

Ex vivo

1) PC111 significantly reduces blister formation in two different ex vivo model of pemphigus

Take Home Message

- PC111 is a novel human anti-soluble Fas Ligand monoclonal antibody for the treatment of the rare autoimmune skin disease pemphigus
- PC111 differentiates over the existing broad immunosuppressive treatments, targeting a molecule downstream of the immune system
- PC111 displays a local site of action, ensuring efficacy with a reduced potential for side effects

References