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

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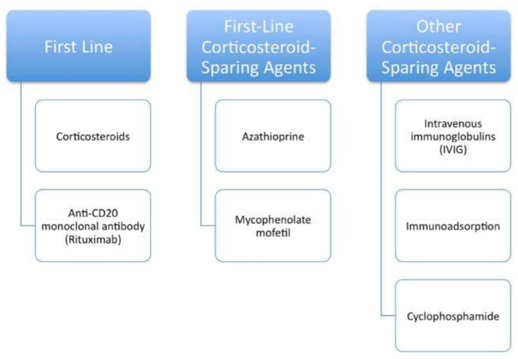
The disease: PEMPHIGUS

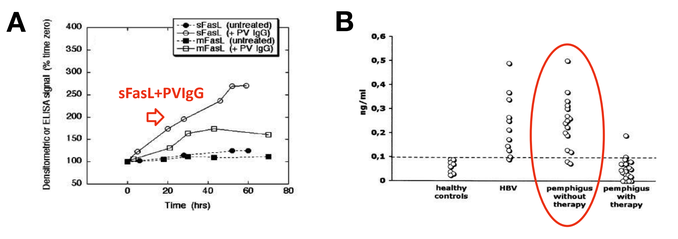
HIGH UNMET MEDICAL NEED

- **Chronic, debilitating** and **life-threatening** condition
- Diagnosed in middle aged persons
- Treated with generalized immunosuppressants (severe side effects, relapses) (*Murrell et al, 2019)*

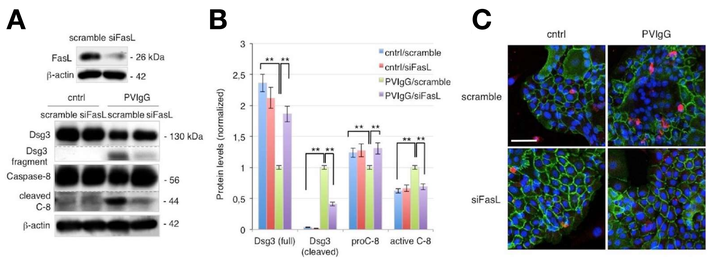


- **Mortality rate 5-15%** due to treatment side effects, estimated to be 3,3 times higher than among age- and sex-matched controls.

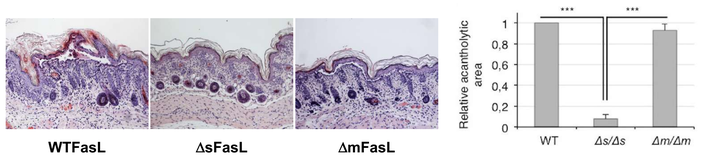
ROLE OF SOLUBLE FASL IN PEMPHIGUS



- 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)

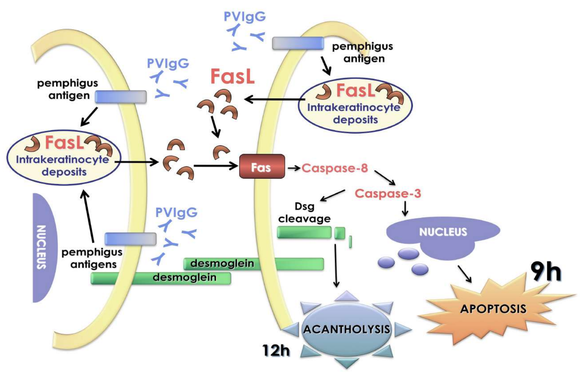


- FasL-silenced keratinocytes are protected from PVIgG-induced desmoglein-3 (Dsg3) cleavage and activation of caspase-8 induced in vitro (A, B). Moreover caspase-3 (in red) is not activated in siFasL keratinocytes upon PVIgG treatment (C) (*Lotti et al, 2018*).



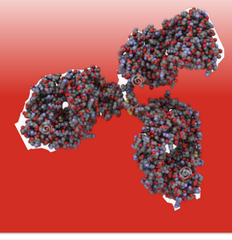
- Soluble FasL is essential for the process of blister formation in pemphigus. Indeed, animals KO for the sFasL (ΔsFasL) are protected from PVIgG-induced acantholysis, unlike WT mice and animals that are KO for membrane FasL (ΔmFasL) (*Lotti et al, 2018*).

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



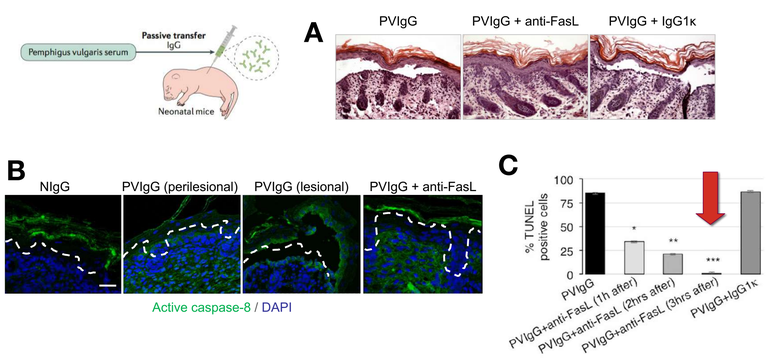
- **Maintain complete remission**
- **Steroid sparing or steroid avoiding**
- **Safe for chronic administration**
- **Avoiding long term immunosuppression**

Results

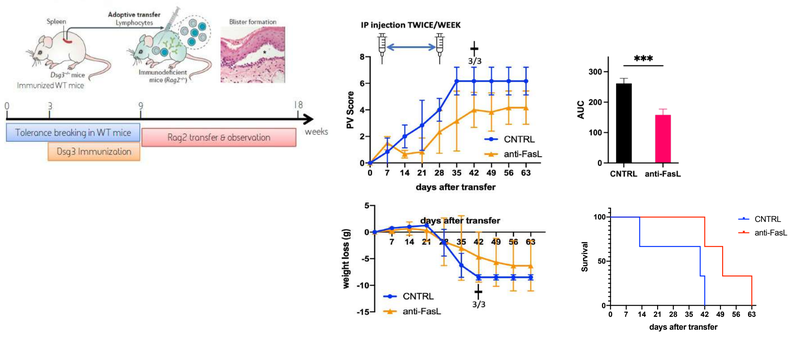
PRELIMINARY RESULTS

In vivo

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



(II) 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



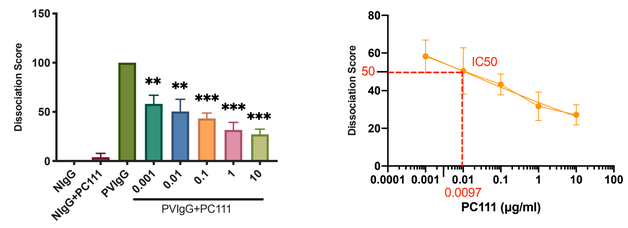
THE PRODUCT: PC111

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

PC111 EFFICACY IN PEMPHIGUS

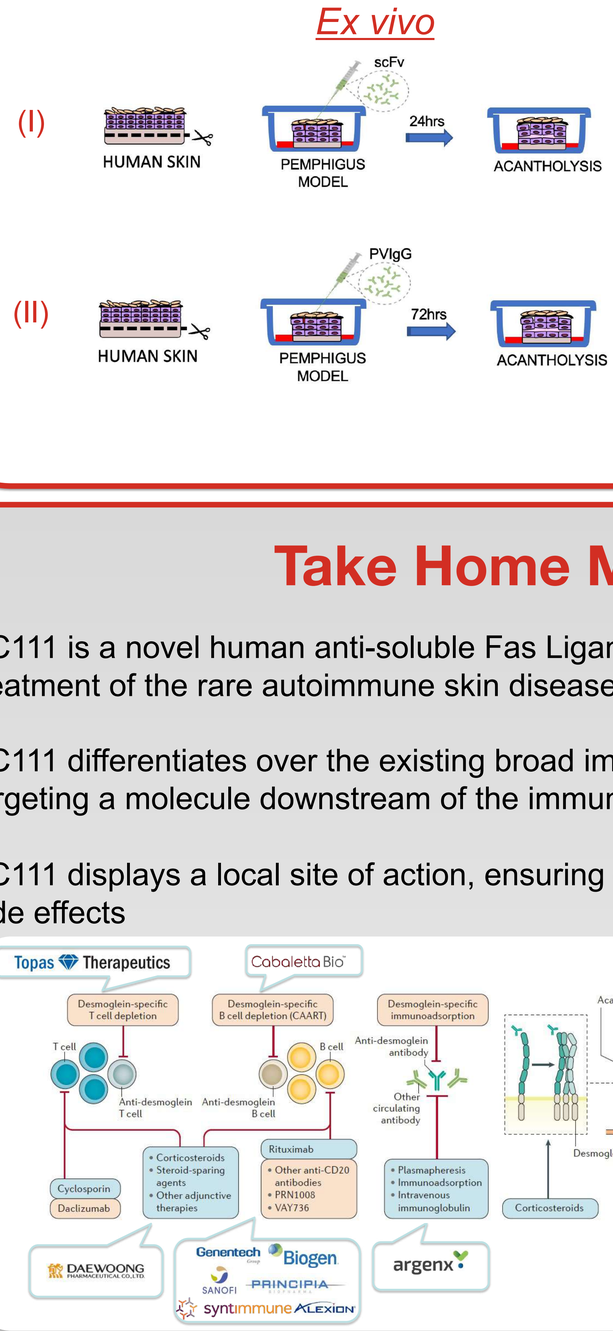
in vitro

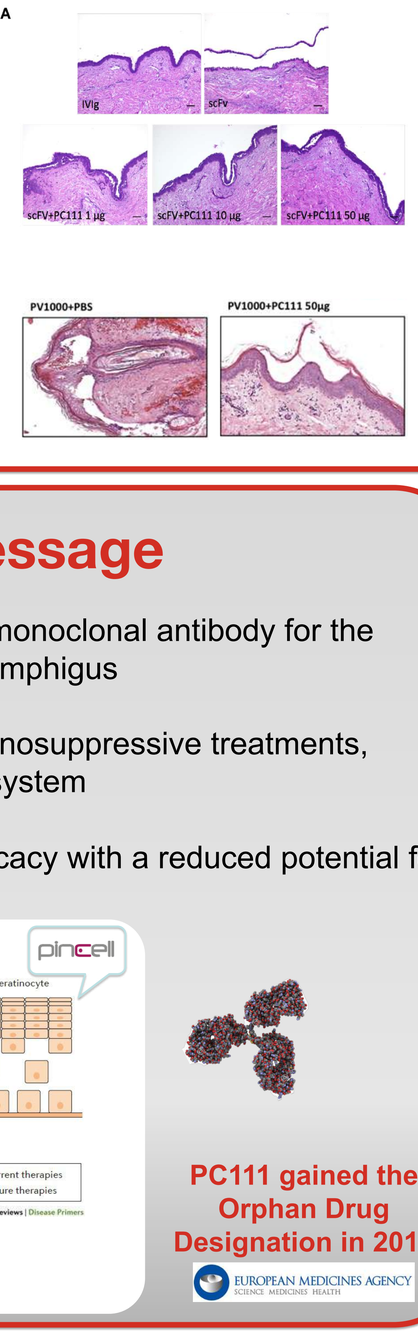
PC111 inhibits sFasL-mediated acantholysis induced by PVIgG treatment with an IC50 of 0.0097 μg/ml (nM concentration)

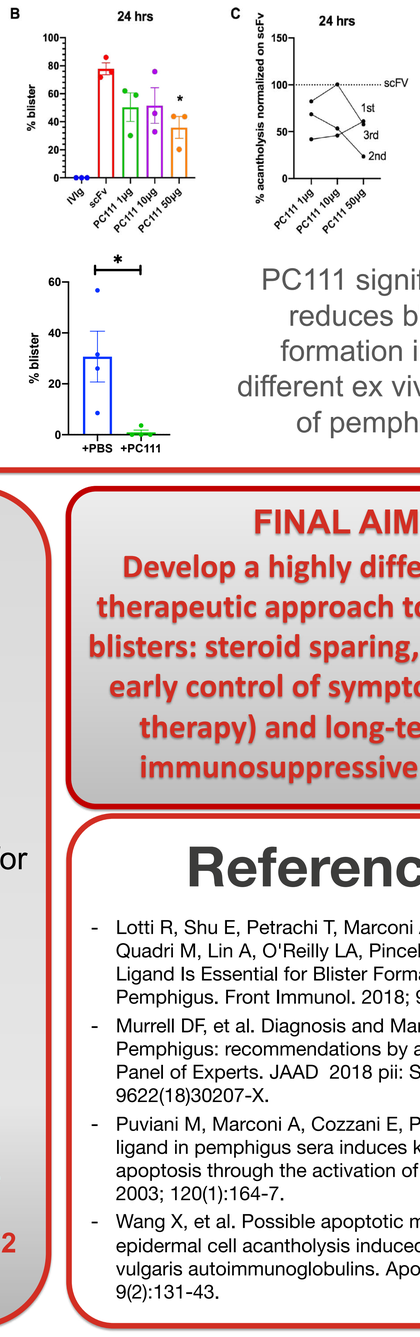


PC111 EFFICACY IN PEMPHIGUS

Ex vivo







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

PC111 gained the Orphan Drug Designation in 2012

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FINAL AIM

Develop a highly differentiated therapeutic approach to block skin blisters: steroid sparing, suitable for early control of symptom (bridge therapy) and long-term non-immunosuppressive therapy

References

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