pincell
Innovation in Dermatology

PC111

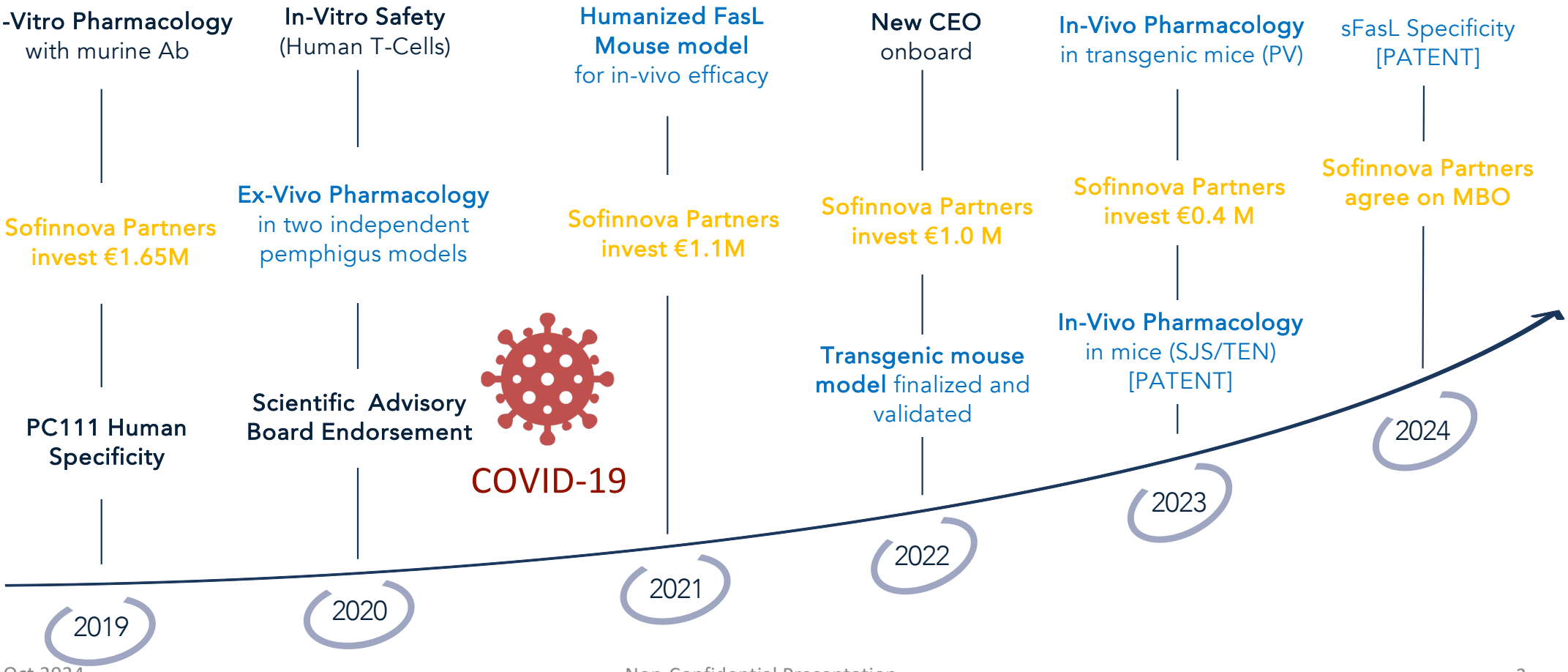
A novel, First In Class , fully human anti-FasL mAb for the treatment of Pemphigus, SJS/TEN and other underserved skin disorders

Executive Summary

- PinCell, academic spin-off of the University of Modena-Reggio Emilia (Italy) previously **seed funded** by Sofinnova
- **Novel target in skin blistering diseases (hu-FasL)** using a fully human monoclonal Ab (PC111) with a unique, non-immunosuppressive MoA
- **Targeting two undertreated orphan indications**
  - Pemphigus: 300,000 patients worldwide, one approved treatment with high unmet medical need and a 5-15% mortality
  - Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN): 5,000-10,000 patients, no approved treatment and up to 30% mortality
  - Combined blockbuster potential, with upside in other indications with significant underserved needs

We aim to develop a First-in-Class innovative therapy for rare skin blistering diseases

Main Achievements



Experienced Team and Board of Directors

Tony Amato, MD
CEO

- Former CEO/CMO Betaglue Technologies
- Former Director CTC Pol. Gemelli, Rome
- Former Sigma Tau Development Director
- > 30 years in healthcare industry

Carlo Pincelli, MD
Co-Inventor, CMO

- Professor of Dermatology, Chief Laboratory of Cutaneous Biology at University of Modena and Reggio Emilia for 25 years
- Proven track record in basic and clinical research

Brydon Bennett, PhD
CSO

- >25 yrs. of experience in pharmaceutical discovery
- Previously at Signal Pharmaceuticals and since 2000 at Celgene (I&I section) until 2018.
- Projects he has championed are currently in all 3 phases of clinical development

Roberta Lotti, PhD
Project Manager & Senior Researcher

- Biotechnologist and Clinical Pathologist with almost 20-yr. experience in research
- Development of several pemphigus models *in-vitro, ex-vivo* and *in-vivo*

Tony Amato, MD
Chairman & CEO

- Former CEO/CMO Betaglue Technologies
- Former Director CTC Pol. Gemelli, Rome
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Co-Founder, Co-Inventor

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- Proven track record in basic and clinical research

Scientific Advisory Board

Distinguished panel of experts in SJS/TEN, Pemphigus and FasL biology

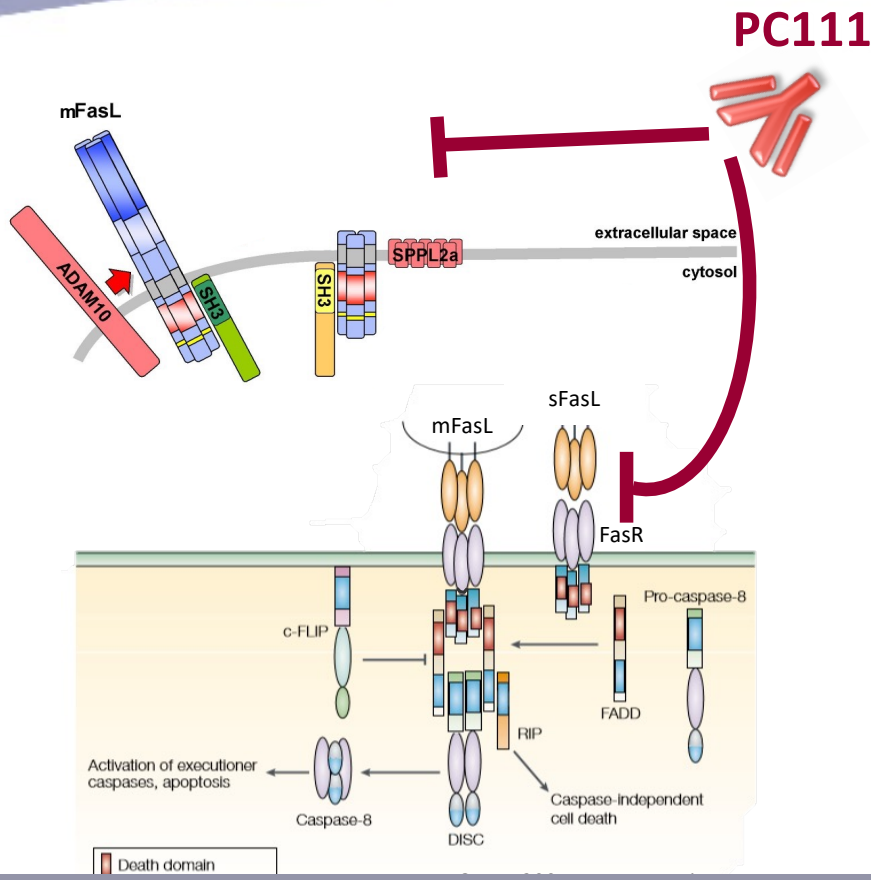







Donna Culton, MD, PhD	**Associate Professor of Dermatology, Associate Director, Clinical Trials Unit**	University of North Carolina, Chapel Hill, NC
Lars E. French, MD, PhD	**Professor and Chairman Department of Dermatology and Allergy**	University Hospital, Munich
Michael Rosenblum, MD, PhD	**Associate Professor of Dermatology**	UCSF, San Francisco CA
Ann M. Rothstein, PhD	**Professor of Medicine**	University of Massachusetts Medical School, Worcester MA
Animesh A. Sinha, MD, PhD	**Associate Professor of Dermatology**	University of Buffalo, Buffalo, NY
Eli Sprecher, MD, PhD	**Director Department of Dermatology; Deputy Director R&D**	Tel Aviv Medical Centre, Tel Aviv
Victoria P. Werth, MD	**Chief, Dermatology Professor of Dermatology**	University of Pennsylvania, Philadelphia, PA
Riichiro Abe, MD, PhD	**Professor of Medicine**	Niigata University, Japan

The Target - FasL/Fas Pathway



Fas Ligand (CD95L, CD178)

- Type II transmembrane protein, member of TNF family
- Expressed on immune cells (activated T cells, NK cells), immune privileged tissues and tumours as membrane-bound FasL (**mFasL**)
- Active as homotrimer, can be processed to a soluble form **(sFasL)** by metalloproteinases during several disease conditions

Fas Receptor (CD95, Apo1)

- Member of the TNF and NGF families, with broad distribution

Role of FasR/mFasL binding-induced cells apoptosis in:

- Immune cells homeostasis, to limit T cells expansion after antigen elimination
- Maintaining immune privilege in specific tissues

Role of FasR/sFasL binding-induced cells apoptosis in:

- Driving blister formation (acantholysis) in keratinocytes

Waring et al 1999, Immunology and Cell Biology (mod.)

PC111 binds specifically and with high affinity to sFasL blocking apoptosis

The Product - PC111 Overview

PC111

Anti-human FasL mAb

- Human monoclonal anti-human FasL antibody [IgG4, k]
- Novel, non-immunosuppressive Mode of Action relevant in the pathogenesis of several skin blistering disorders
- Target Selectivity: specific for sFasL, no off- targets from 6000 membrane proteome array (including mFasL)
- High binding affinity (KD<200pM) to human soluble FasL

The Product - PC111 Overview

PC111

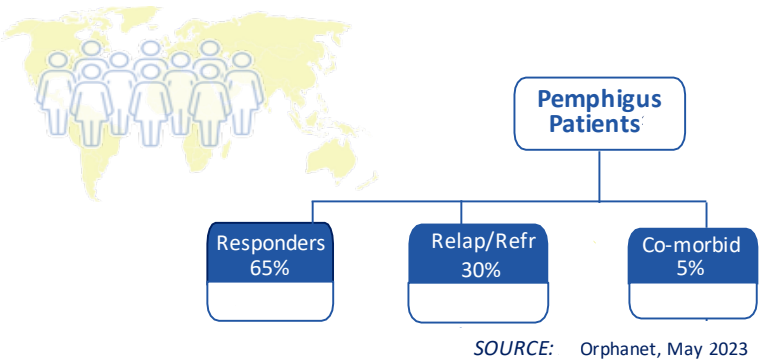
Anti-human FasL mAb

- Optimal solubility, allows reaching high concentrations (>70mg/ml)
- Low in-silico immunogenicity
- Drug product manufacturing: small scale-up to 2.4 grams in transient transfected HEK and CHO; observed yield > 600 mg/L
- Species Cross Reactivity (sFasL): no binding to mouse, partial binding to dog; primate sequence identity with human is 97%

PC111 is a suitable candidate for further pre-clinical and clinical development

Pemphigus – An Unmet Medical Need

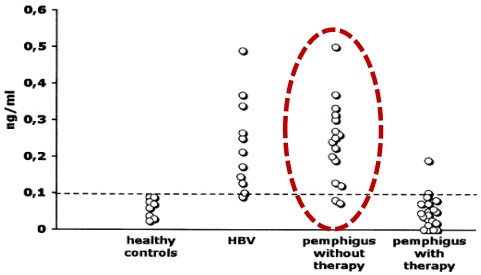
	Pemphigus[1]
Characteristics	Autoimmune disease, with blisters and erosions of skin/mucosae; diagnosed in middle age
Course of disease	Chronic, debilitating and life-threatening Overall mortality 5-15% due to side effects (3x controls)
Epidemiology[2]	Prevalence 1,92/10,000 worldwide Target population ~300,000 patients worldwide
Approved Treatment	Rituximab plus steroids (2020)
Unmet Medical Needs	Relapsing (up to 60%) and refractory patients Severe side effects of extended immune-suppression
Market Size by 2030	~1B$ growing at a CAGR of 8%[3]



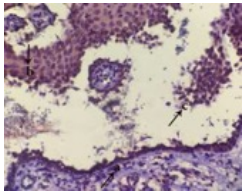
References - 1) UpToDate (Wolters Kluwer, Mar 2023); 2) Orphanet (Mar 2023); 3) Data Bridge Market Research (2022)

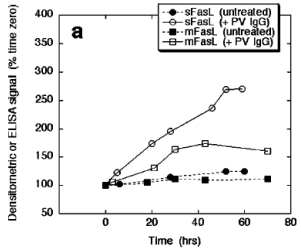
FasL in Pemphigus - Strong Validation

- FasL is increased in **sera** of pemphigus patients (Puviani et al, 2003)
- FasL positive cells are present in the **skin** of patients with oral pemphigus (Deyhimi and Alishahi, 2018)
- In dogs with pemphigus foliaceous, the **Fas pathway** was significantly over-expressed compared to healthy controls by micro-array analysis on **skin** (Starr et al, 2024)
- PV-IgG's induce **FasL release** from keratinocytes *in-vitro* (Wang et al, 2004)
- **FasL released** from keratinocytes upon PV-IgG treatment is responsible for acantholysis through caspase-8 activation followed by Dsg-3 cleavage (Lotti et al, 2018)
- **FasL downregulation** counteracts PV-IgG effect, as shown by FasL silencing in human keratinocytes *in-vitro* (Lotti et al, 2018)



Detection of FasL in pemphigus sera

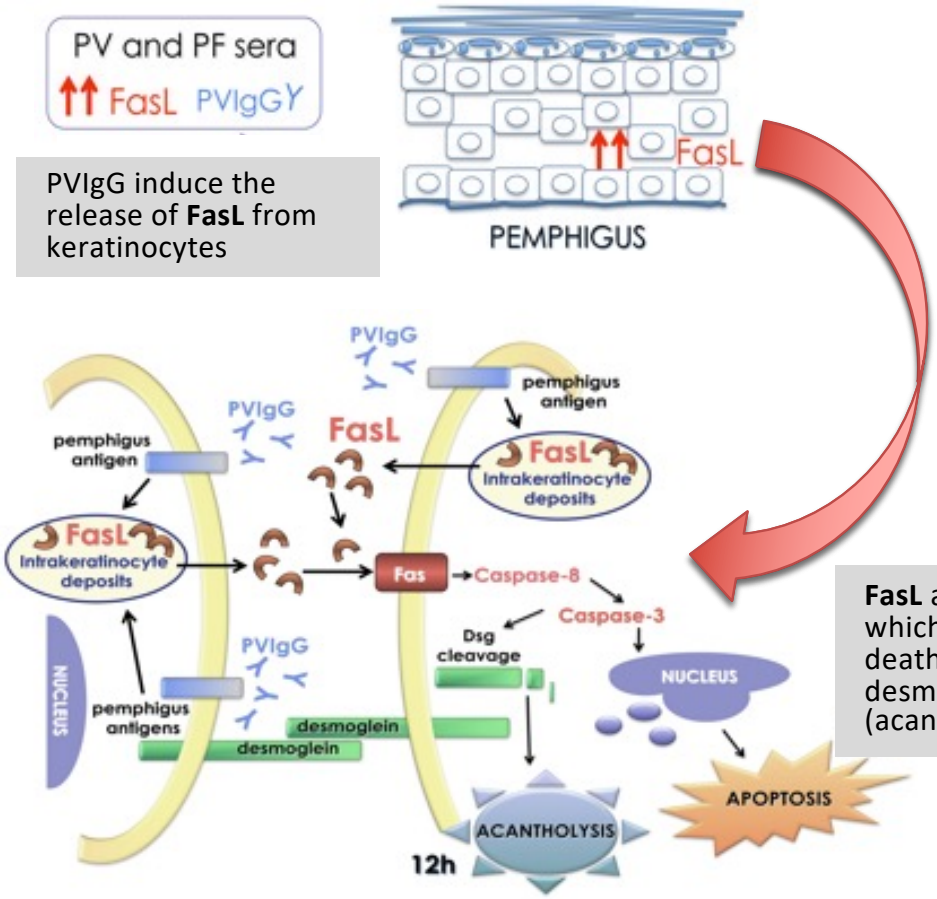

FasL-positive cells in oral PV skin



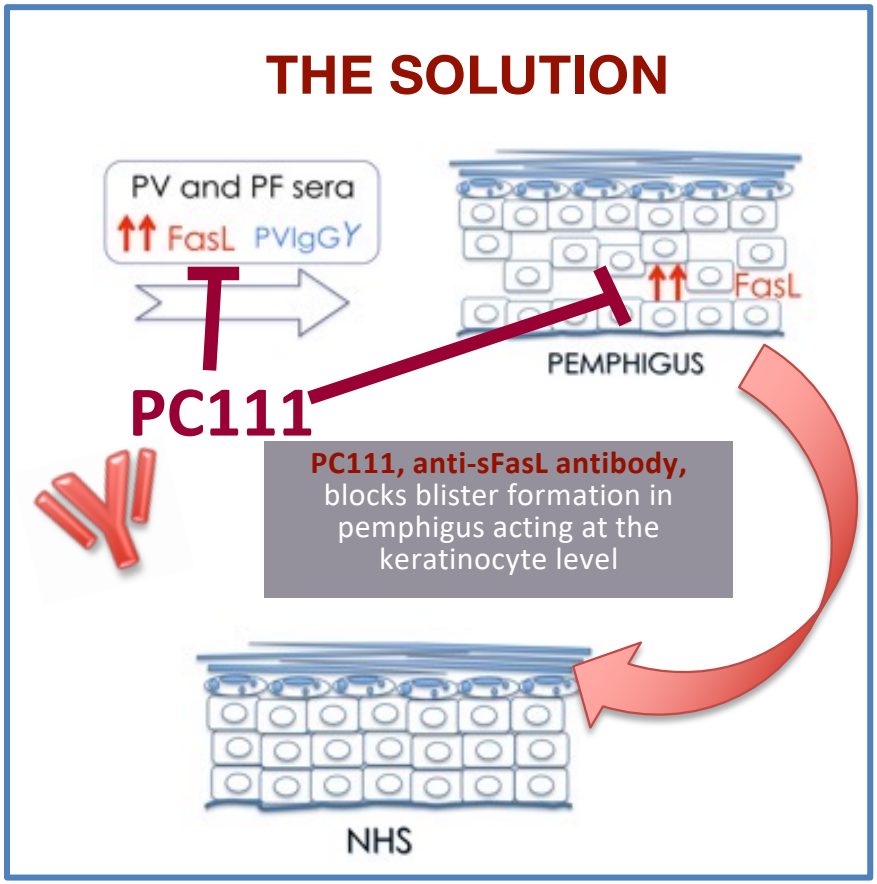
PV-IgG induce FasL release from keratinocytes

Potential breakthrough: prevent skin blistering by blocking FasL

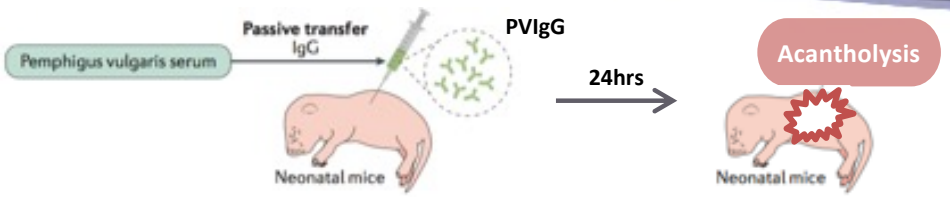
FasL in Pemphigus – Role of PC111

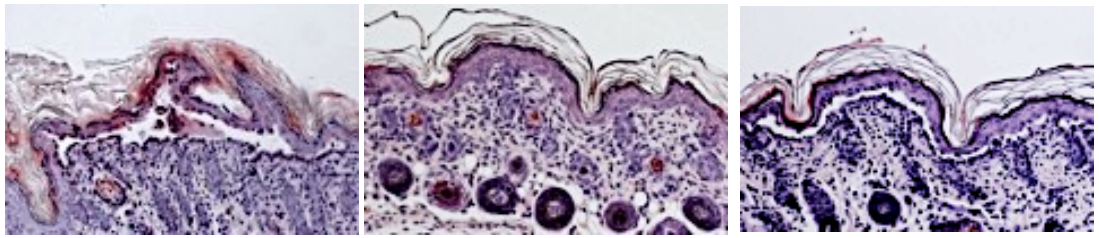


FasL activates caspases, which in turn induces cell death (apoptosis) and desmoglein degradation (acantholysis)

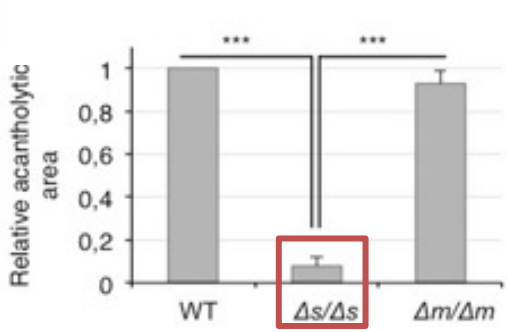


FasL is essential for blister formation *in-vivo*



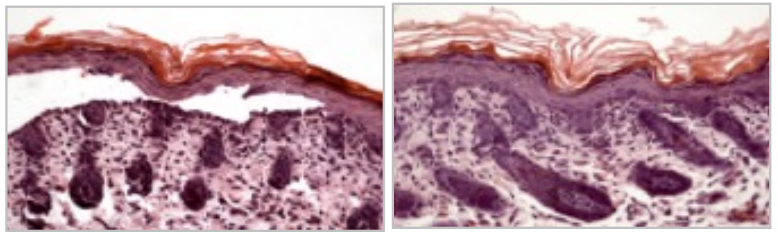


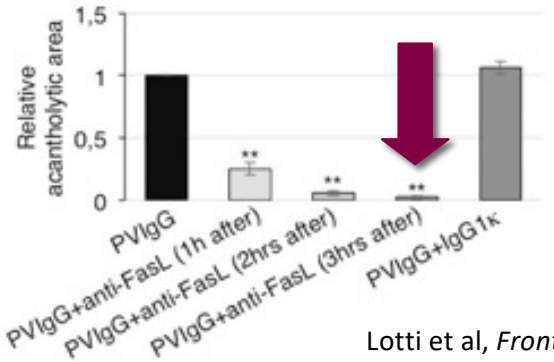
WT **Δs/ΔsFasL** **Δm/ΔmFasL**



PV-IgG

PV-IgG
+ anti-FasL Ab (3hrs after)





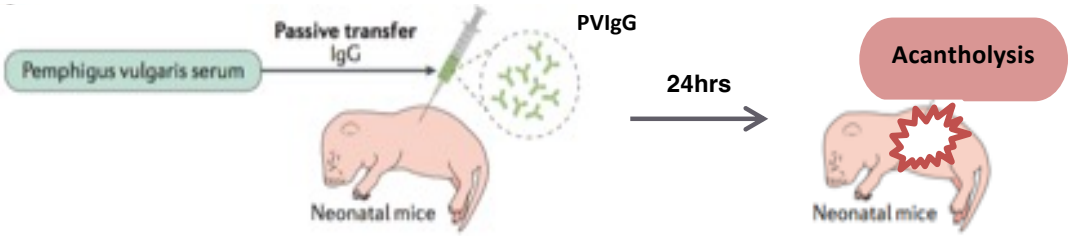
Lotti et al, *Frontiers Immunol, 2018*

Only mice lacking sFasL fail to develop blisters upon injection of PV-IgG's

Administration of an anti-murine FasL Ab blocks blister formation

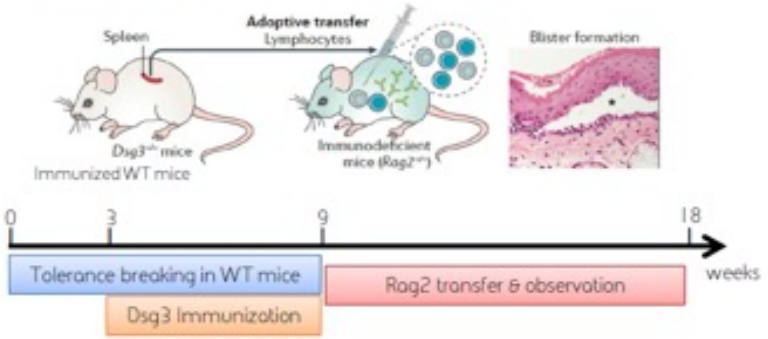
FasL blockade is effective in PV models

Passive pemphigus mouse model



- Anti-murine FasL mAb **blocked blister formation** in a dose-dependent manner in a neonatal passive transfer pemphigus mouse model

Active pemphigus mouse model



- Anti-murine FasL mAb induced a **rapid PV score reduction** in an adult active pemphigus model
- Anti-FasL mAb showed a **less dramatic weight loss** vs. control or steroid-treated groups
- Anti-FasL mAb **increased survival rate** in treated animals

PC111 in Pemphigus: PoC Studies

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In-vitro

- PC111 is effective in **preventing FasL-dependent acantholysis** of normal human keratinocytes in a **dose dependent** manner *(Lotti et al, Front Immunol 2023)*
- In activated human primary T-cells, PC111 did not affect mFasL dependent apoptosis

Ex-vivo

- PC111 was tested in 2 independent ex-vivo pemphigus human skin models:
  - It significantly **reduced blister formation** by 50% in a severe PV model
  - It dramatically **blocked blister extent** in a milder pemphigus model
    (Lotti et al, Front Immunol 2023)

In-vivo

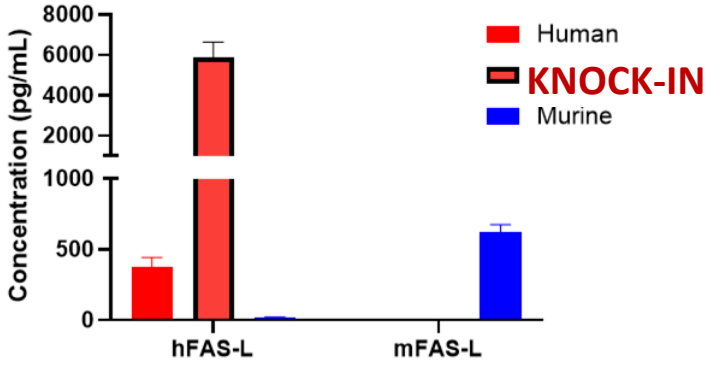
- We have successfully developed a proprietary *in-vivo* platform for PC111 testing: the first **FasL humanized mouse model**
  - PC111 **efficacy confirmed** in such mice with passive transfer of PV-IgG's
- **PK/PD study** completed

FasL Humanized Mouse Model

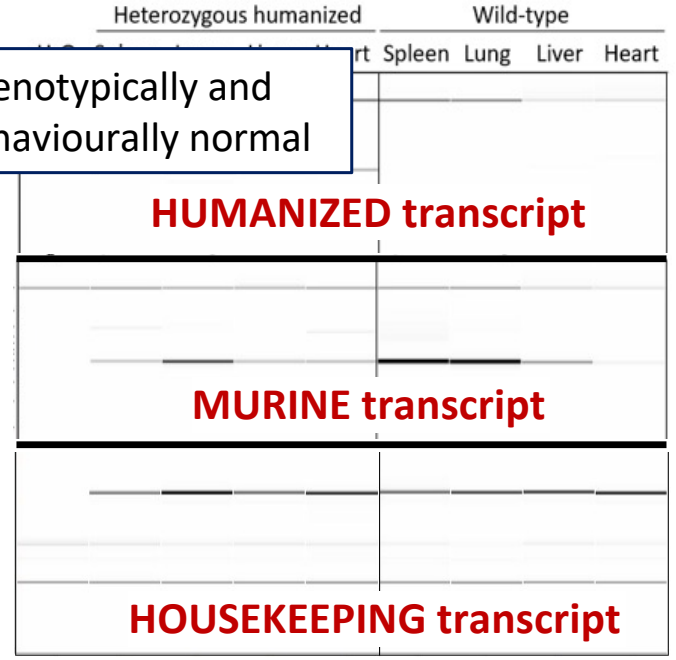
First **HUMANIZED FASL MOUSE MODEL** for *in-vivo* pre-clinical studies

C57BL/6N-Fasl$^{tm1(FASL)/Geno}$

Phenotypically and behaviourally normal



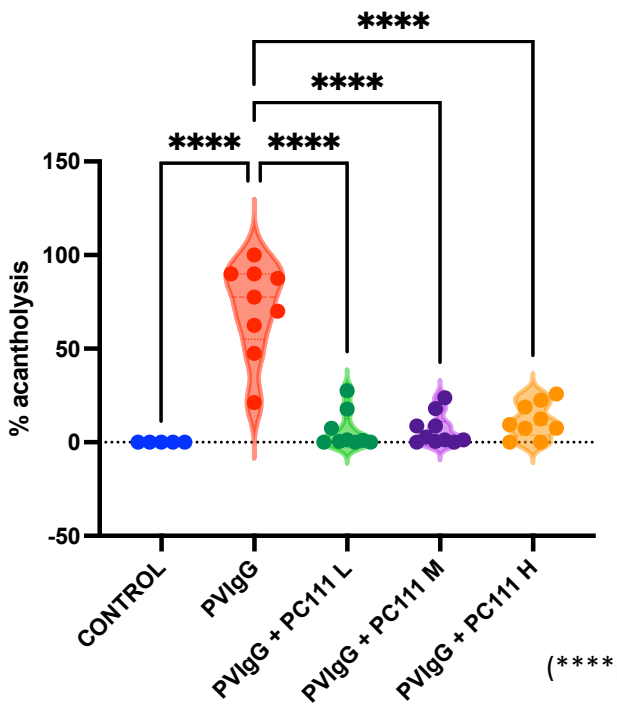
Human soluble FasL protein quantified by ELISA



Confirmed in 2 different HET animals

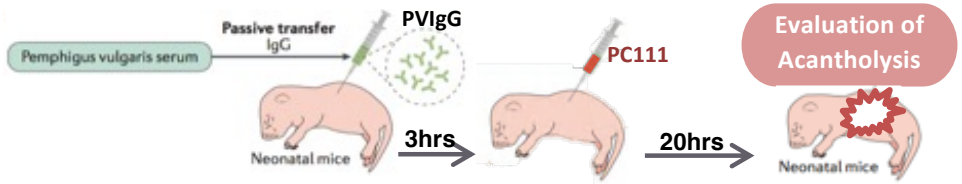
Independent Review by an SAB Member

PC111: Studies in Humanized FasL Mice



(****p<0.0001, Dunnett adj.)

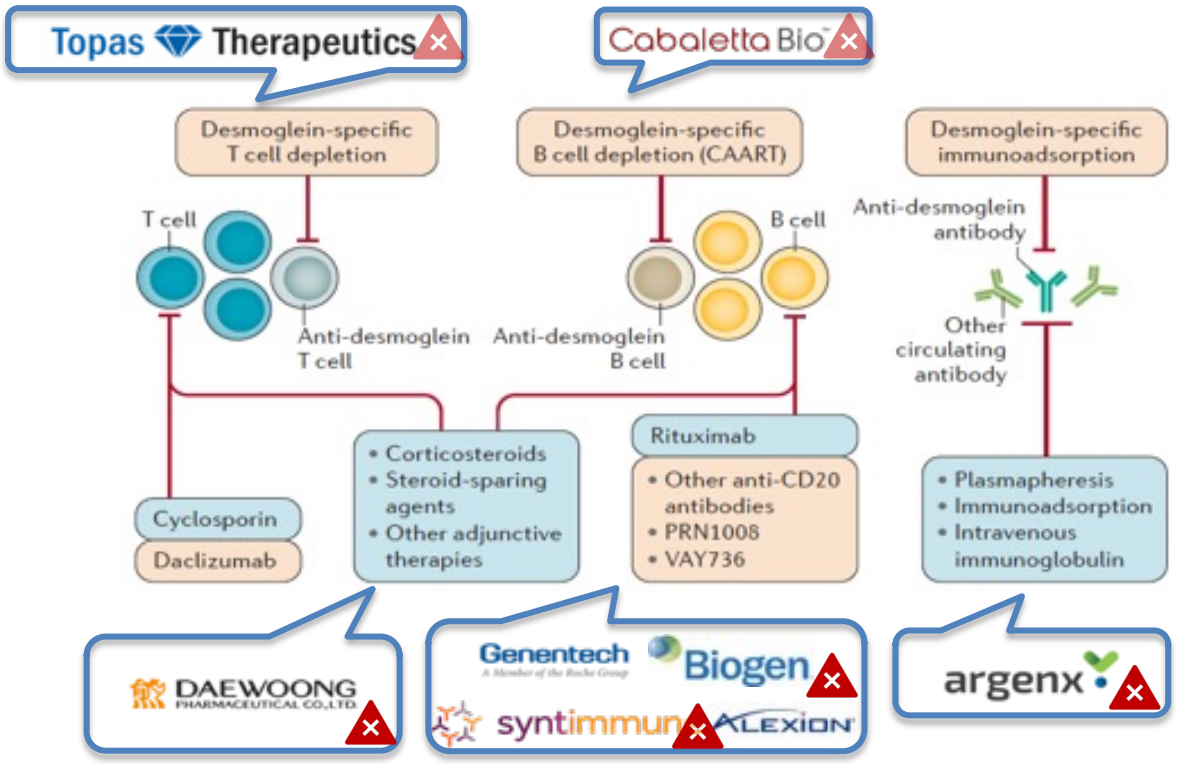
Neonatal PVIgG Transfer Study (Gold Standard)

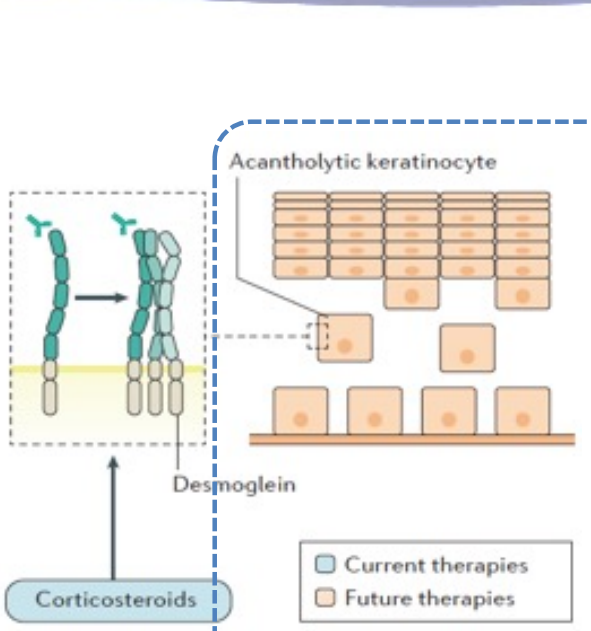


- **University of Modena - CSSI**
  - PV-IgG's from patients used to induce disease
  - Three PC111 doses used for dose-response relationship (Low, Medium, High)
  - PC111 **blocks blister formation (>90%)** in a validated model of treatment

***In-vivo* studies in a proprietary humanized FasL mouse model fully confirm PC111 effect in inhibiting sFasL and blocking blister formation**

PC111 in Pemphigus: Unique Mode of Action





PC111 blocks blister formation in pemphigus acting at the **keratinocyte level**, down-stream of the immune system

Nat Rev Dis Primers. ; 3: 17026. doi:10.1038/nrdp.2017.

Clinical development stopped or currently suspended

References - ClinicalTrials.gov (Aug 2024); GlobalData (Apr 2023)

Targeted disease-modifying treatment, with rapid onset and better safety than immunosuppressants

PC111: a significant step forward *vs.* competitors

Molecule[7]	Description	Current stage
PRN 1008	**Bruton's Tyrosine Kinase (BTK) inhibitor** Inhibits B cell activation and antibody induction.	**Phase III** **STOPPED for pemphigus**
Ianalumab/VAY736	**Fully human antibody against BAFF-R (B-cell activation factor receptor)** Depletes peripheral B-cells and inhibits production of clones in germinal centers	**Phase II** **STOPPED for pemphigus**
Efgartigimod/ARGX-113	**Fc fragment anti-human FcRn (Fc Neonatal Receptor)** Blocks IgG recycling and increases IgG clearance	**Phase III** **STOPPED for pemphigus**
Orilanolimab/SYNT001	**Humanized IgG4 mAb to block IgG interactions with neonatal Fc receptor (FcRn)**	**Phase I/II** **DISCONTINUED for pemphigus**
DSG3-CAART	**Autologous chimeric autoantibody receptor (CAAR) T cell therapy** to target B cells producing autoAbs to DSG3	**Phase I** **SUSPENDED for pemphigus**
TPM203	Nano-particle based therapeutic for **T-reg stimulation**	**Phase I** **SUSPENDED for pemphigus**

PC111: Positioning in Pemphigus

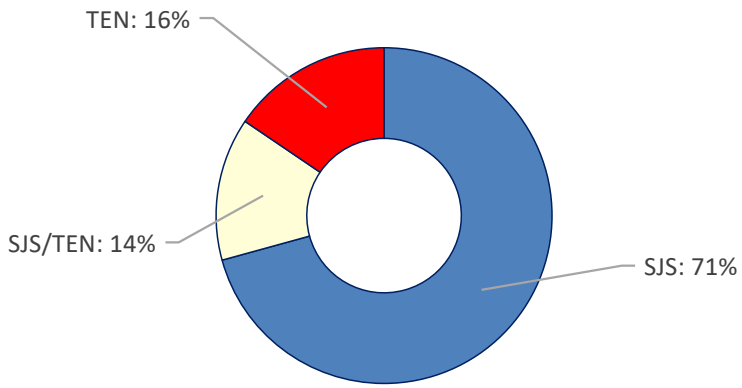
- First targeted therapy
  - Non-immunosuppressive, acting downstream of the immune system
  - Local site of action at the keratinocyte level
  - Rapid mode of action
- First-line therapy w/wo steroids
  - Potential combination with Rituximab (separate/complimentary MoA's)
  - Bridge therapy before Rituximab achieves clinical remission
  - Potential steroid sparing/avoiding effect
- Second-line therapy in relapsing/refractory patients (35% overall)
  - Quicker induction of remission
  - Potential steroid and/or immunosuppressant sparing/avoiding effect

Puviani et al, J Invest Dermatol, 2003; Lotti et al, Curr Pharm Biotechnol, 2012; Lotti et al, Front Immunol 2018

SJS/TEN – Life-Threatening, No Approvals

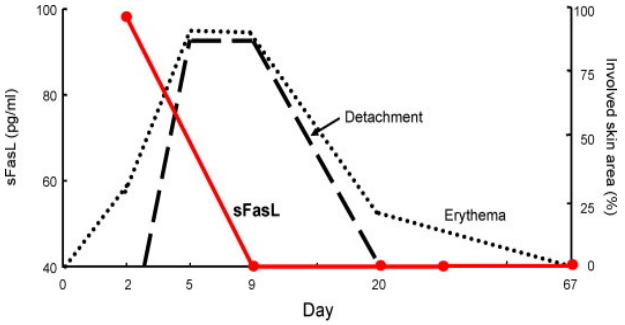
	Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis[1]
Characteristics	Toxic dermatosis associated with drugs or infections (SJS<10% BSA, TEN>30% BSA); onset at any age
Course of disease	Acute and often life-threatening Overall mortality 8% (≥30% in TEN patients)
Epidemiology[2]	Incidence 1-2/1,000,000 worldwide Target population ~5,000-10,000 patients worldwide
Approved Treatment	No approved treatment ICU/burn unit care setting needed
Unmet Medical Needs	Improve survival of severe form and prevent less severe form progression; decrease hospital costs
Market Size by 2030	> 8B$ growing at a CAGR of 4%[3]

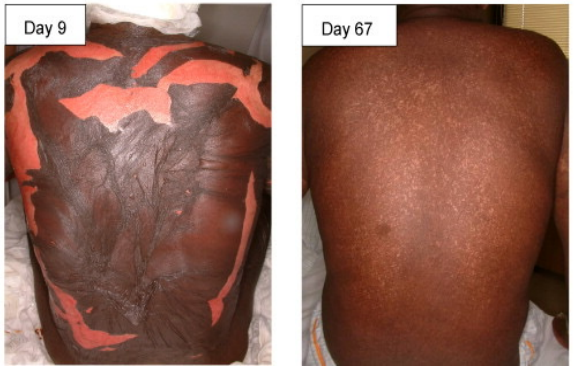
Incidence of Different Forms of SJS/TEN (Hsu et al, 2012)



References - 1) UpToDate (Wolters Kluwer, Mar 2023); 2) Orphanet (Mar 2023); 3) Data Bridge Market Research (2022)

FasL in SJS/TEN: Strong Validation

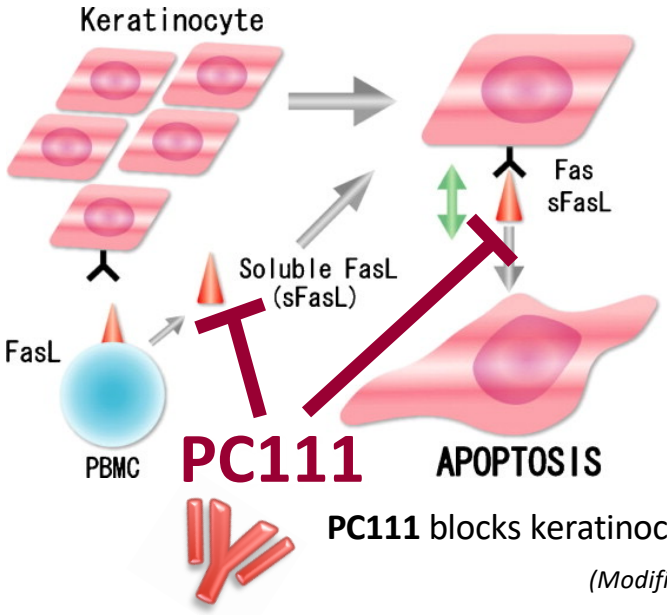




- The clinical course of the disease is **closely related to the change of serum sFasL**
- Soluble FasL is detected **before and at the onset** of the disease, to decline few days later

(Abe R. at al, 2008)

- Skin detachment is due to extensive death of keratinocytes *(Abe R. at al, 2003)*
- Aberrant activation of the immune system by the causative drugs **causes SJS/TEN through high levels of sFasL**



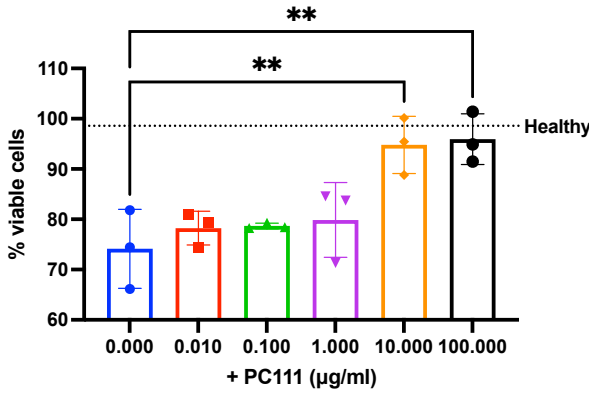
PC111 blocks keratinocyte apoptosis

(Modified from Abe R. at al, 2008)

PC111: PoC Data in SJS/TEN

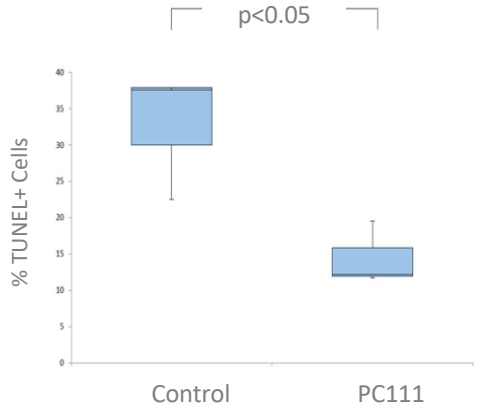
In-vitro Study (Prof. R. Abe) NIIGATA UNIVERSITY

- SJS/TEN donor serum confirmed to have elevated sFasL
- PC111 **rescues viability of HaCaT cells** exposed to serum
- Dose-dependent response (≥10 µg/mL)



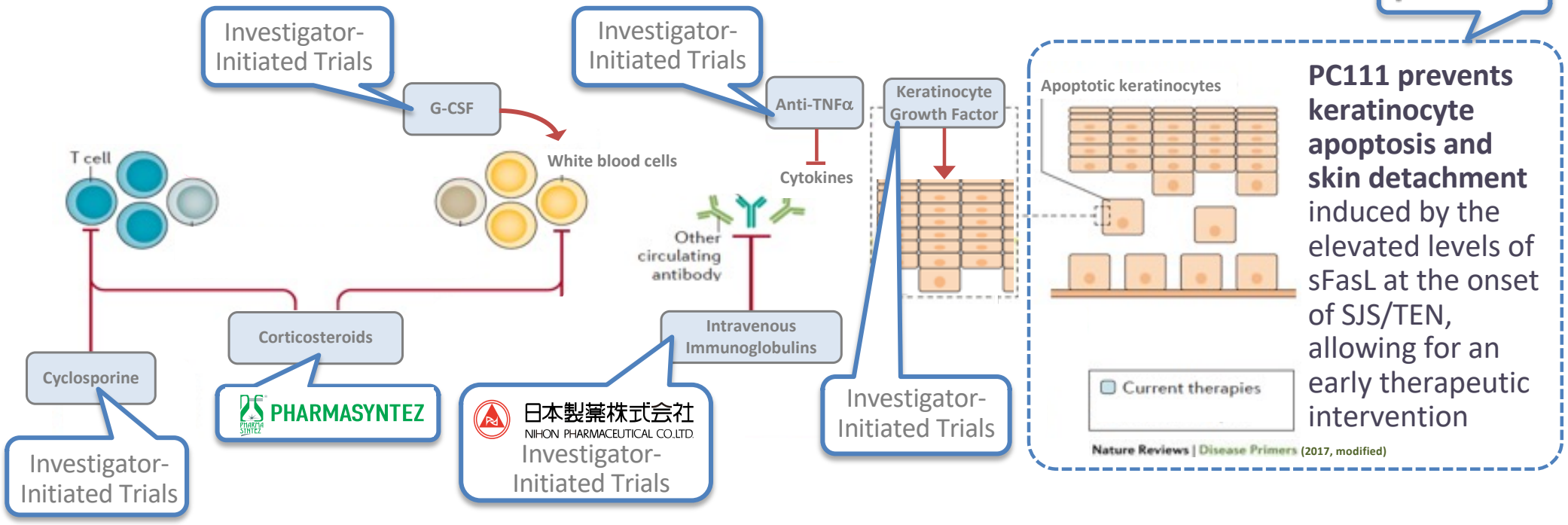
In-vivo Study (Prof. R. Abe)

- **Prevention of conjunctivitis** in an established SJS/TEN model induced by patients' PBMCs plus acetaminophen
  - PC111 single-dose at day 0 and every 2 days up to day 12
- PC111 group had a significantly ($p<0.05$) lower percent of **TUNEL positive cells** and reduced hyperemia of conjunctiva
  (Saito et al, J Invest Dermatol 2024)



PC111 in SJS/TEN: Highly Differentiated

- No molecules or targeted therapy currently in development for SJS/TEN



PC111 prevents keratinocyte apoptosis and skin detachment induced by the elevated levels of sFasL at the onset of SJS/TEN, allowing for an early therapeutic intervention

References - 10) ClinicalTrials.gov (Apr 2023); 11) GlobalData (Apr 2023)

Novel, non-immunosuppressive MoA and the first targeted therapy in active development

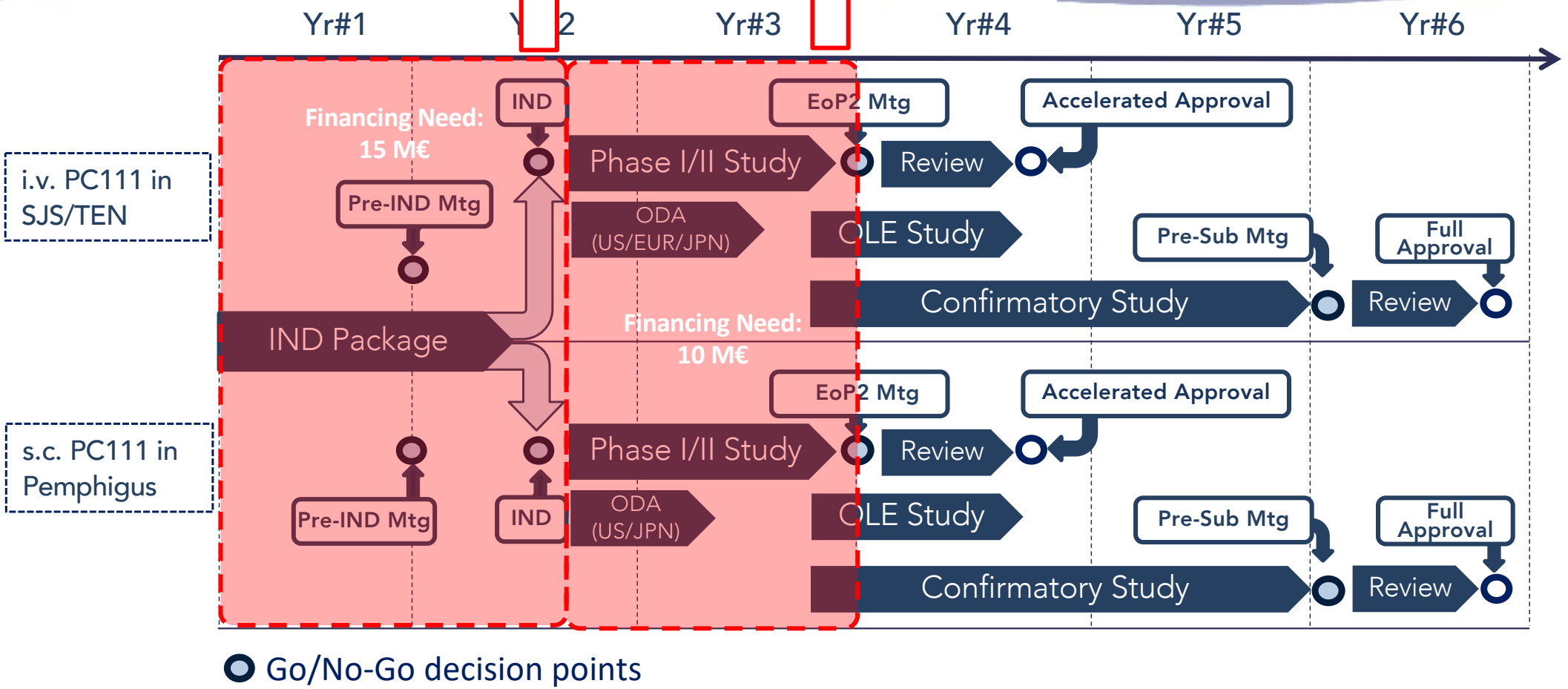
PC111: a significant step forward

- No approved treatment currently available for SJS/TEN

Recent Meta-Analyses	Treatments	Results	Conclusions
Torres-Navarro et al. JEADV 2020	IVIg + Cyclosporin + Steroids	Combination associated with less deaths than predicted by SCORTEN	No treatment achieved a significant result
Singh et al, Skin Therapy Letter 2022	IVIg + Cyclosporin + Steroids + Etanercept	Combination reduces mortality	Complex data and conflicting results: no treatment can be recommended
Jacobsen et al, Cochrane DB 2022	Steroids, IVIg, Cyclosporin, Etanercept	No difference vs. no therapy, except for Etanercept* vs. steroids = slight mortality reduction	*CI not confirmed More studies needed
Tsai et al, JAAD 2020	Steroids, IVIg, Cyclosporin, Etanercept	Steroids + IVIg = reduced mortality Etanercept and Cyclosporine= inconclusive data	Low numbers, more studies needed
Krajewski et al, Burns 2022	Steroids, IVIg, Cyclosporin, Etanercept	Etanercept associated with lowest mortality Most negative outcome for IVIg	No randomization or double- blind control
Wang et al, JCI 2017	Etanercept vs. Steroids	Improved outcome: reduced skin-healing time, decreased mortality	Randomized trial needed

Novel, non-immunosuppressive MoA and the first targeted therapy in development for SJS/TEN

Development Plan Strategy



Additional Indications for PC111

Disease	Epidemiology	Rationale
Drug-induced hypersensitivity syndrome (DIHS)[7]	• Yr. incidence 1.2-6.0/1,000,000 • 20% mortality rate	• High sFasL levels in patients sera correlating with disease severity
Drug reaction with eosinophilia and systemic symptoms (DRESS)[8]	• Yr. incidence 0.1-1.0/1,000 (anticonvulsants therapy) • 10% mortality rate, (acute hepatitis)	• High sFasL levels in patients sera correlating with disease severity
Erosive Oral and Genital Lichen Planus[9] (risk for Squamous Cell Ca.)	• Prevalence varies from 0.5-2.6% (oral) to 0.1-1.7% (vulvar) worldwide	• High sFasL levels in patients sera
Acute Respiratory Distress Syndrome[10]	• Yr. incidence: 3 million cases worldwide • Functional and cognitive impairment in 50% patients • Mortality rate up to 40%%	• High FasL levels in plasma, bronchial lavage, and lung tissue • Correlation between sFasL levels and death
Rheumatoid Arthritis[11]	• 1% general population worldwide	• High sFasL levels in joints and synovial fluids • sFasL stimulates synoviocyte proliferation
Systemic Lupus Erythematosus[12]	• Incidence: 5/100.000 persons/years • Mortality rate of 22.2 per 1000 person-years	• sFasL levels are markedly increased • High sFasL is related with active disease
Sjogren syndrome[13]	• Incidence: 0.5-1% general population	• High sFasL levels in in saliva and sera • No correlation with disease severity

References – 7) Hama N, J Allergy and Clin Immunol Pract 2022 ; 8) Yang F, Eur J Dermatol 2018; 9) Didona D, Front Immunol 2022;
10) Martin TR, Proc Am Thorac Soc 2005; 11) Kim WU, Arthritis Res Ther 2006; 12) Vincent FB, BMJ 2020; 13) Vincent FB, Clin Exp Rheumatol 2019

Intellectual Property, Market/Data Exclusivity

- **Remedies for pemphigus containing anti FasL antibodies**
  - WO 2010/066914 (filed 12/2009, granted)
- **Anti-Fas Ligand (FasL) Antibodies in the Treatment of SJS/TEN** NEW
  - PCT Application WO2024/200287 (priority date: 03/2023, pending)
- **Antibodies with high target affinity and specificity to FasL** NEW
  - US Application no. 63/568,580 (filed 03/2024, pending)
- **Other Applications under development**
- **Orphan Drug Designation (EUR) in Pemphigus**
  - EU/3/12/956 (granted)
- **Orphan Drug Application (USA, JPN) in Pemphigus (planned)**
- **Orphan Drug Application (EUR, USA, JPN) in SJS/TEN (planned)**
  - Rare Pediatric Disease Priority Review Voucher can be claimed (FDA)
- **Biologics Data Exclusivity (EUR, USA, JPN, RoW)**

Conclusion

- **Novel, fully human mAb with a unique non-immunosuppressive MoA** in skin blistering diseases with significant medical needs, large addressable markets and rising CAGR's
- **Patent and EUR-ODD granted** in pemphigus, with **additional patent families** and/or **ODA's** submitted or in preparation also for SJS/TEN
- **Upside potential** in other underserved diseases with high levels of FasL
- **Safety and efficacy data** obtained from PoC studies in validated pemphigus and SJS/TEN models, using a **proprietary humanized FasL mouse** platform
- Ready to start **IND-enabling studies**
- Looking to exploit PC111 potential in SJS/TEN and pemphigus, either through a **Series A round** of 15-25M€ (until IND or Ph1/2 studies readouts), or the asset **co-development/acquisition**

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