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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

OVERVIEW

- PC111 is a fully human IgG4 monoclonal Ab binding to the human FasL, a **novel target in skin blistering diseases,** with a unique, non-immunosuppressive MoA
- **Main Orphan Indications**
  - Pemphigus (300,000 patients worldwide) with high medical need (5-15% mortality); addressable market (2030) >1Bn$
  - Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), 5,000-10,000 patients worldwide with up to 30% mortality; addressable market (2030) >8Bn$
- **IP Status:** patent in pemphigus granted world-wide; SJS/TEN application submitted; additional IP in preparation
- **Orphan Drug Designation** in pemphigus (EUR), with US/JPN application planned; OD application in SJS/TEN planned
- **Funded** by Sofinnova for a total of 2.8M€

OUR ACHIEVEMENTS

- **Relevance of FasL** as a valid target in pemphigus, SJS/TEN
- **Chemical-physical properties** of PC111 suitable for manufacturing scale-up and human testing
- **Pemphigus PoC efficacy** of PC111 to prevent dose-dependently blister formation in:
  - *in-vitro, ex-vivo* and *in-vivo* models
  - confirmation in *in-vivo* passive PV-IgG pemphigus model (gold standard for the disease) using a **proprietary FasL humanized mouse**
- **SJS/TEN PoC efficacy** of PC111 shown *in-vitro* and *in-vivo* in an established mouse model
- **Safety** profile on T-cell proven *in-vitro*
- Low *in-silico* **immunogenicity** (ADA)
- Development of the **first humanized FasL mouse platform**

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

Executive Team

Tony Amato, MD

CEO

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

Carlo Pincelli, MD

CMO, Co-Founder, Co-Inventor

- 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
- Inventor of 6 derma-related NCEs (1 in Ph. II)

Alessandra Marconi

Co-Founder, Co-Inventor

- Professor of Applications of Medical Biotech at at University of Modena and Reggio Emilia
- Clinical Pathologist with 25-years experience in basic and clinical research in dermatology
- Inventor of 4 derma-related NCEs (1 in Ph. II)

Roberta Lotti, PhD

Project Manager & Senior Researcher

- Biotechnologist and Clinical Pathologist with 10-yr. experience in basic/applied research
- Development and publication of several pemphigus models *in-vitro, ex-vivo* and *in-vivo*

Brydon Bennett, PhD

CSO

- Over 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

Board of Directors

Luigi Costa
Chairman

- Over 25 years of leadership and operational experience in the global pharmaceutical and biotech industry
- Previous CEO of Nordic Nanovector
- Several leadership positions with Amgen and Eli Lilly both in Europe and in the US

Tony Amato, MD
CEO

- Previous CEO/CMO Betaglue Technologies, SpA
- Previous Director Clinical Trial Center Policlinico Gemelli, Rome (Italy)
- Previous CEO Sigma Tau Research Inc, Gaithersburg (MD, USA)
- > 30 years of experience in R&D and life-science industry

Carlo Pincelli, MD
Co-Founder, Co-Inventor

- Professor of Dermatology with 35-yrs clinical and research experience
- Chief of the Laboratory of Cutaneous Biology at the University of Modena and Reggio Emilia for 25 years
- Past-President of the European Dermatology Forum (EDF)
- Honorary Member and former President of the European Society for Dermatological Research (ESDR)

Paola Pozzi
Partner, Sofinnova Partners

- Sofinnova Telethon Fund, Italy's first biotechnology fund focusing on rare and genetic diseases
- Previous Head of the Office of Biotechnology Transfer at Ospedale San Raffaele (Milan, Italy)

Scientific Advisory Board

Distinguished panel of experts in pemphigus, SJS/TEN 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

PC111: Product Overview

PC111

Anti-human FasL moAb

- Fully human monoclonal anti-human FasL antibody [IgG4, k]
- Novel Mode of Action relevant in the pathogenesis of several skin blistering disorders
- High binding affinity (KD<200pM) to human FasL
- Species Cross Reactivity: no binding to mouse, partial binding to dog; primate sequence identity with human is 97%

PC111 is a suitable candidate for clinical development to provide rapid suppression of symptoms and achieve control in uncontrolled situations

PC111: Product Overview

PC111

Anti-human FasL moAb

- Optimal solubility, allows reaching high concentrations (>70mg/ml)
- Drug product manufacturing: small scale-up to 2.4 grams in transient transfected HEK and CHO; observed yield > 600 mg/L
- Low *in-silico* immunogenicity (ADA)
- Toxicokinetics studies enabled by proprietary humanized mouse

PC111 is a suitable candidate for clinical development to provide rapid suppression of symptoms and achieve control in uncontrolled situations

PC111 in Pemphigus

PEMPHIGUS[1]

- Rare autoimmune bullous disease
- Blistering and erosions of skin and mucous membranes
- Chronic, debilitating and potentially life-threatening
- Market size (2030) >1 B$ growing at a CAGR of 8%[2]

EPIDEMIOLOGY[1,3]

- Pemphigus vulgaris (PV, 75%) prevalence
  - 1 to 5/10,000 in EU
  - 0.52/10,000 in US
  - 1.92/10,000 globally
- Pemphigus foliaceous (PF, 25%) prevalence
  - 0.1 to 0.9/10,000 globally
- **Estimated Global Addressable Market: 300,000 patients**
- Diagnosed in middle age (45-55 years)
- Mortality: 5-15% due to treatment side effects (>3x than controls)

UNMET MEDICAL NEED[3]

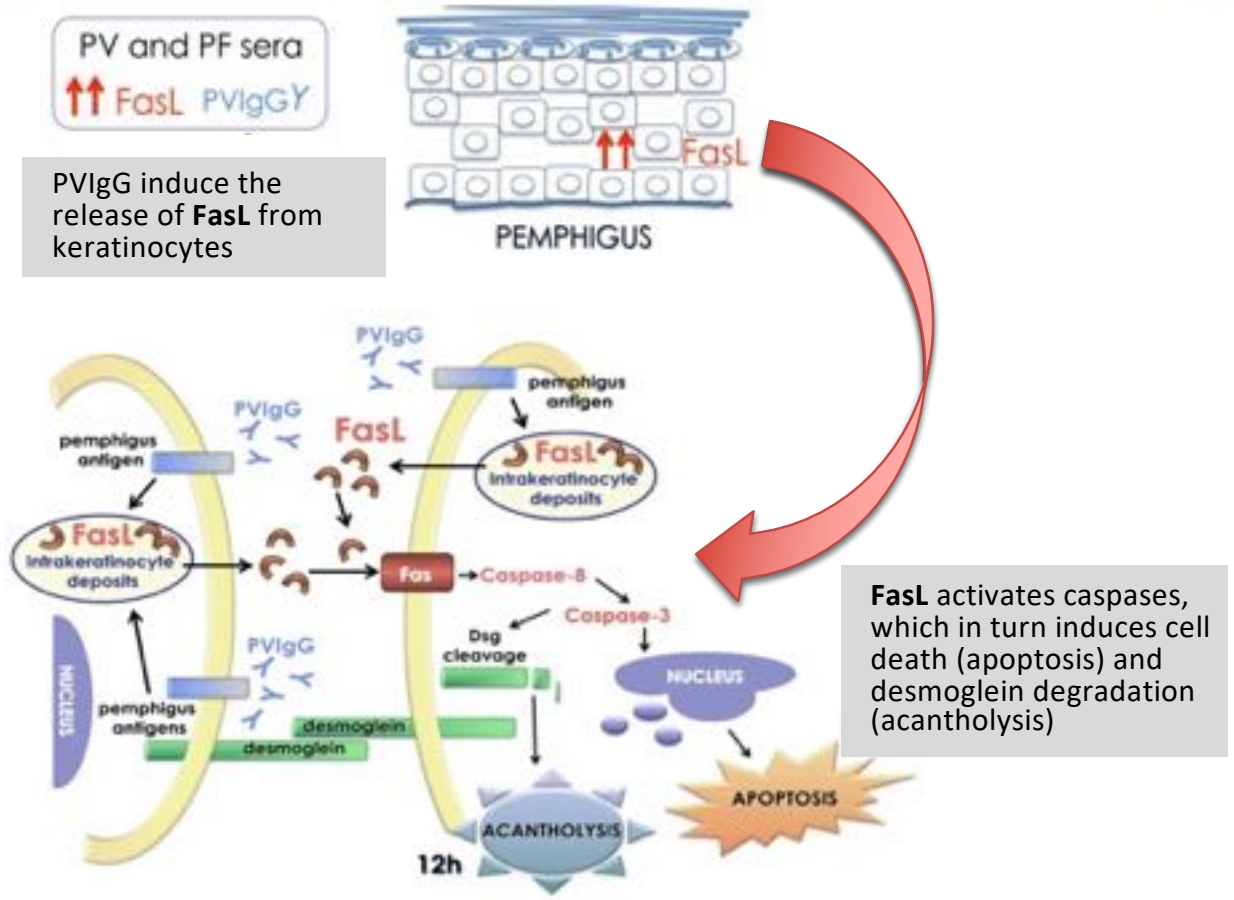
- Approved treatment: i.v. rituximab with glucocorticoids (2020)
- Frequently **relapsing patients**
  - 50-60% of rituximab-treated
  - 89% of steroid-treated
- **Refractory patients**

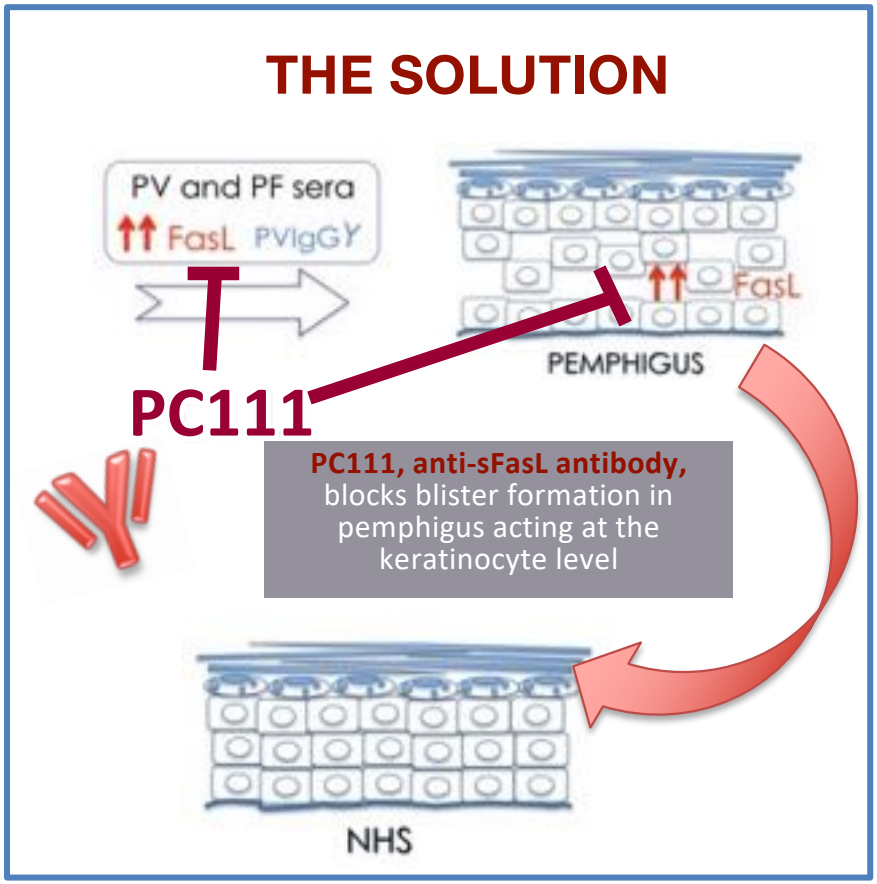
Treatment goals

- Maintain complete remission
- Safety for chronic administration
- Steroid-sparing or steroid-avoiding
- Avoid long-term immunosuppression

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

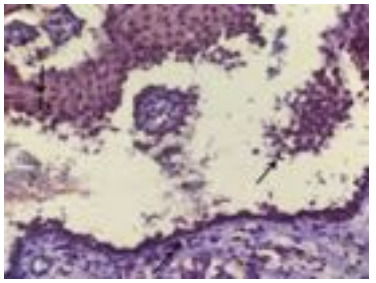
The Target (FasL): Role in Pemphigus





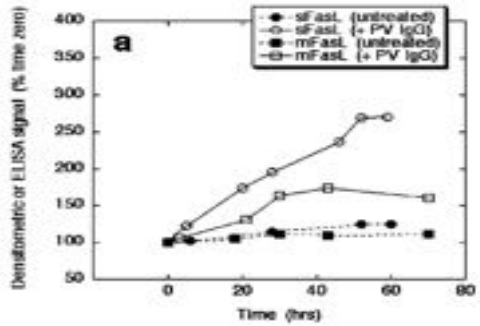
The Target (FasL): Strong Validation

- 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)



FasL-positive cells in oral PV skin

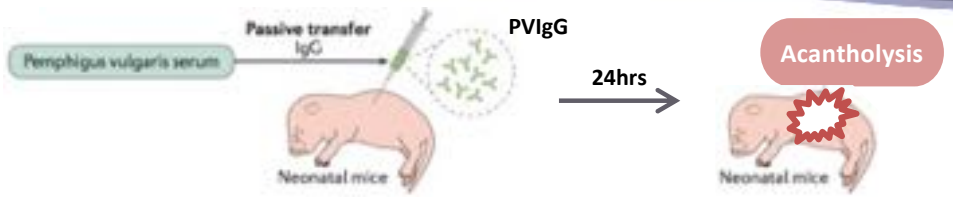
- PV-IgG's induce **FasL release** from keratinocytes *in-vitro* (Wang et al, 2004)
- **FasL released** from keratinocytes upon PV-IgG treatment is responsible for acantholysis through caspase-8 activation followed by Dsg-3 cleavage (Lotti et al, 2018)
- **FasL downregulation** counteracts PV-IgG effect, as shown by FasL silencing in human keratinocytes *in-vitro* (Lotti et al, 2018)

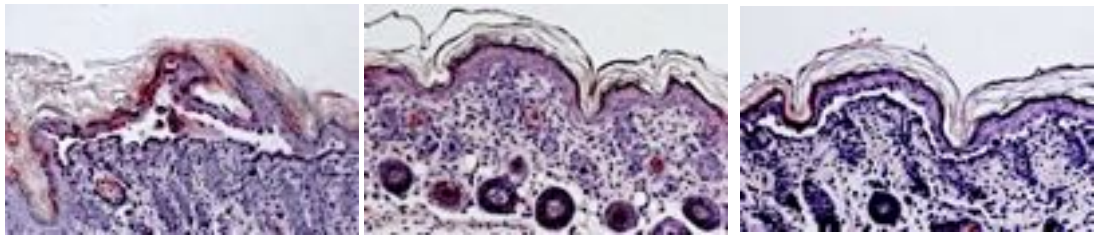


PV-IgG induce FasL release from keratinocytes

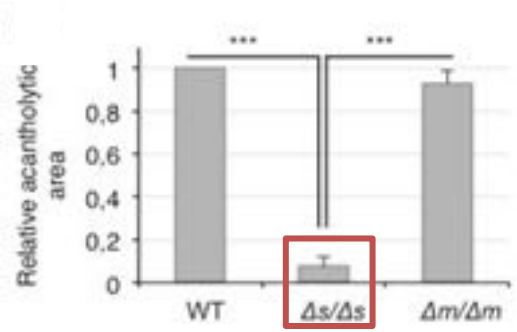
Potential breakthrough: prevent skin blistering by blocking FasL

FasL is essential for blister formation *in-vivo*



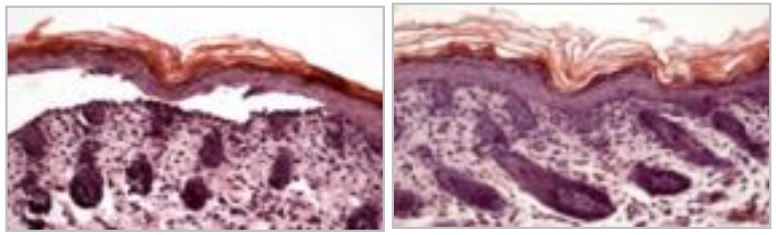


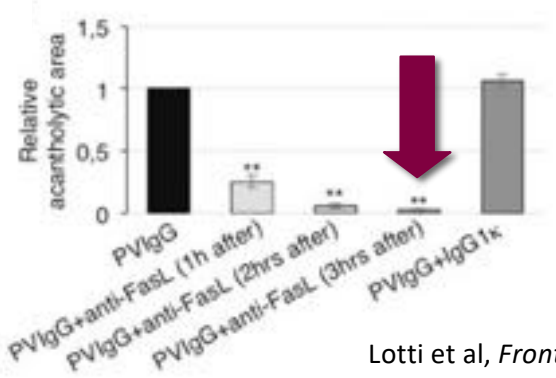
WT **Δs/ΔsFasL** **Δm/ΔmFasL**



PV-IgG

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





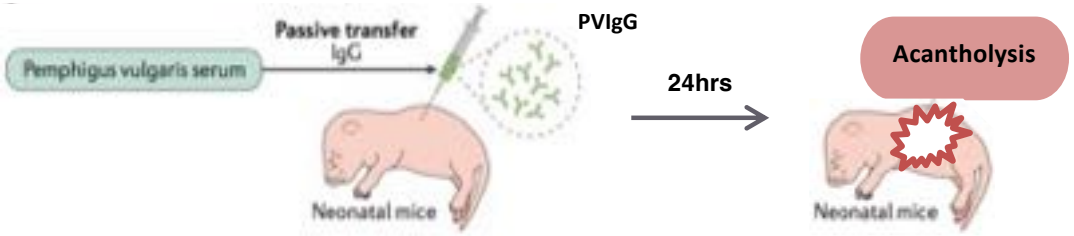
Lotti et al, *Frontiers Immunol, 2018*

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

Administration of an anti-murine FasL Ab blocks blister formation

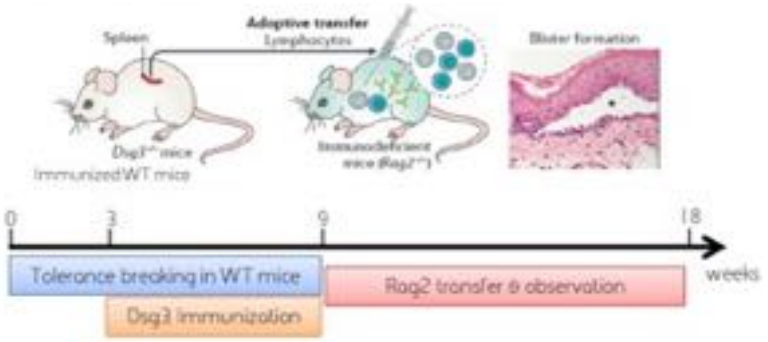
FasL blockade is effective in PV mouse models

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
- 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

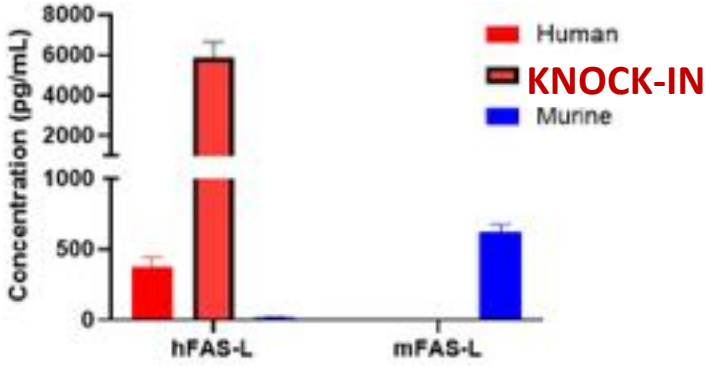
In-vivo

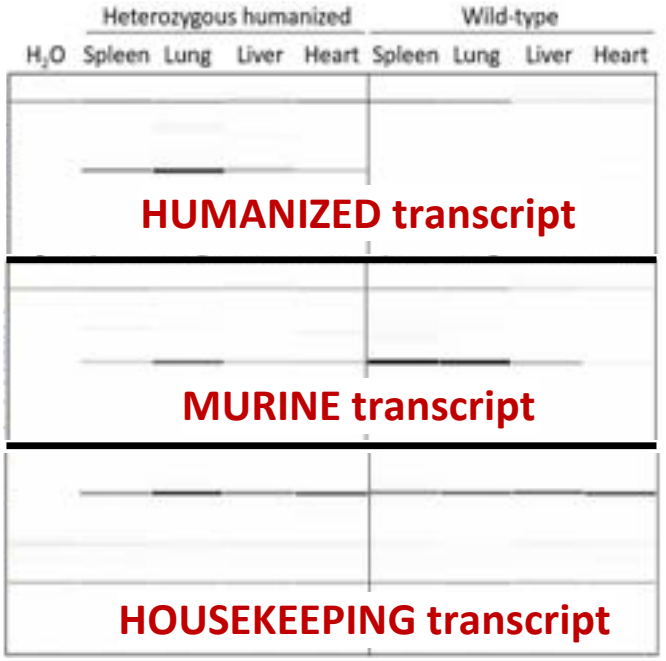
- We have successfully developed a proprietary *in-vivo* platform for PC111 testing: the first **FasL humanized mouse model**
  - PC111 **efficacy confirmed** in such mice with passive transfer of PV-IgG's
- **PK/PD study** completed

FasL Humanized Mouse Model

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

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



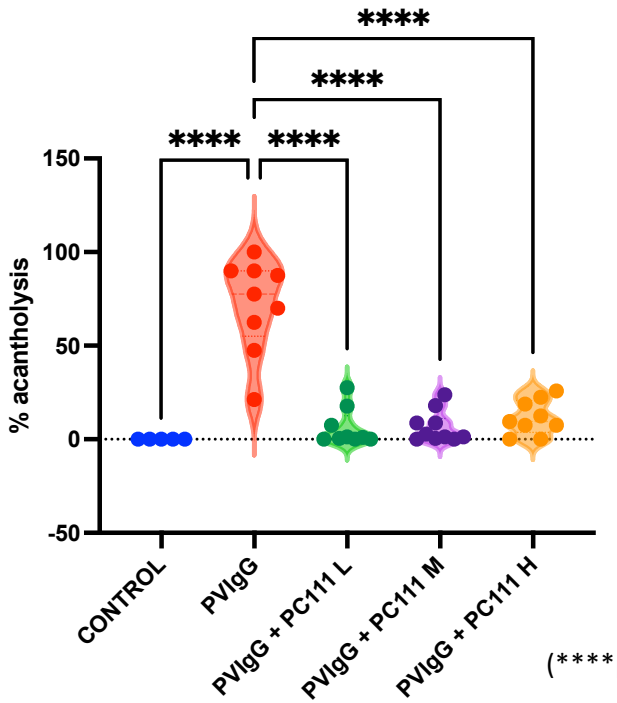


Confirmed in 2 different HET animals

Independent Review by an SAB Member

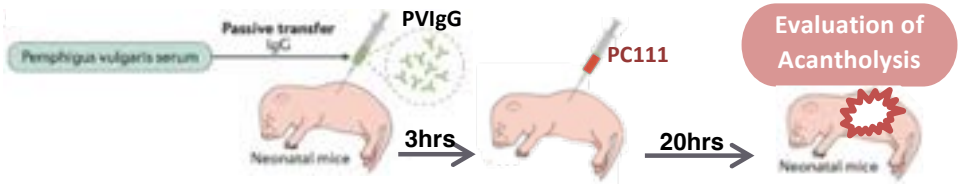
Human soluble FasL protein quantified by ELISA

PC111: Studies in Humanized FasL Mice



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

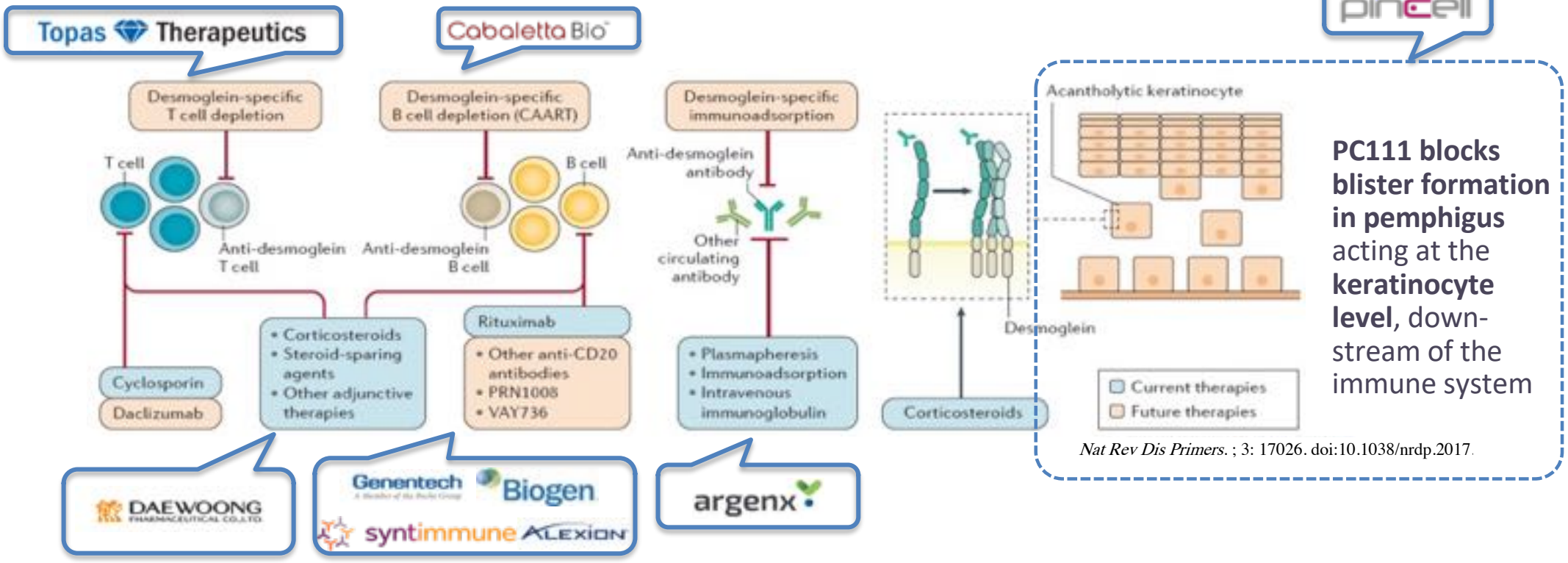
Neonatal PVIgG Transfer Study (Gold Standard)



- **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: Highly Differentiated Asset



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.

Alternative MoA, with rapid onset and better safety than immunosuppressants

PC111: a significant step forward *vs.* competitors in pemphigus therapy

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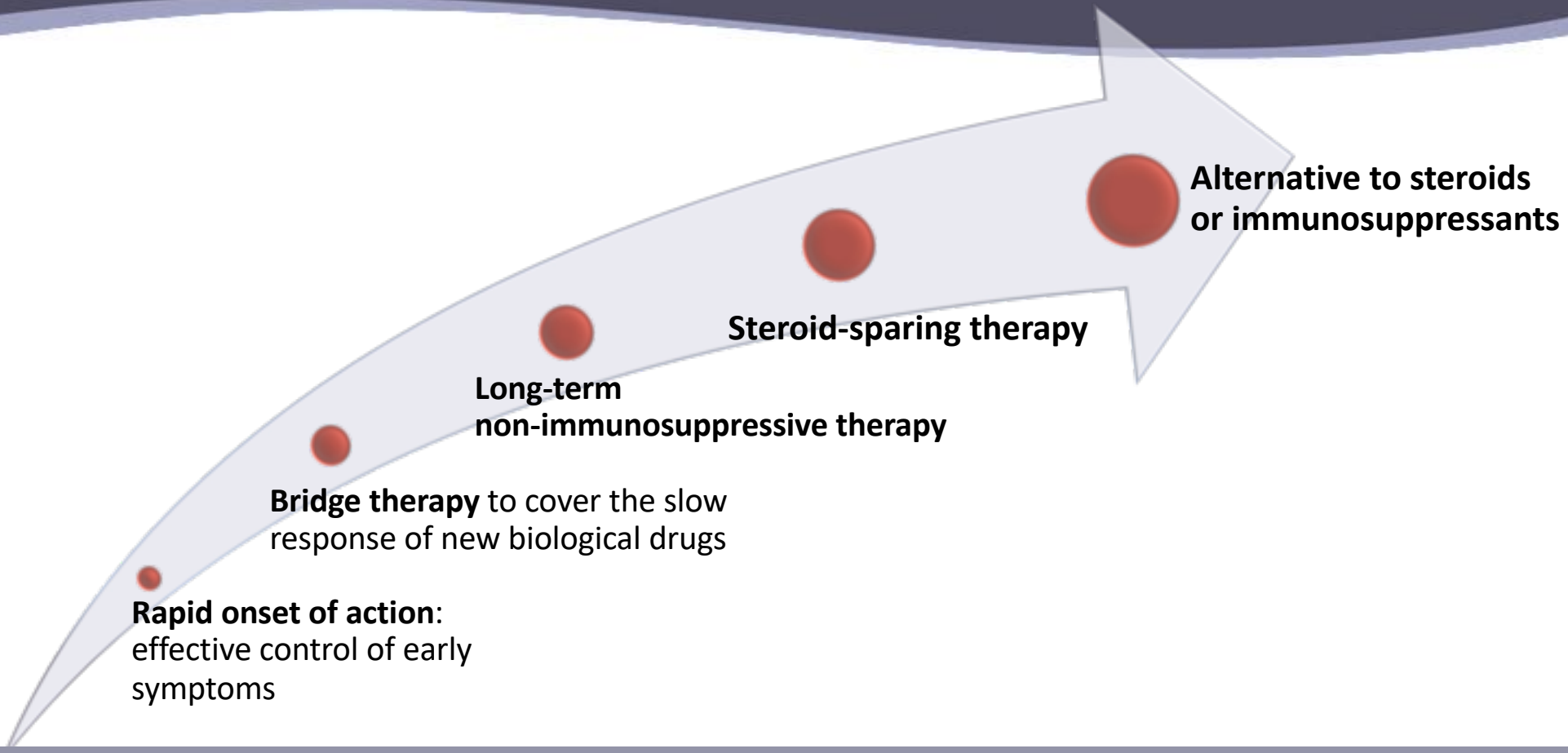
Molecule[7]	Description	Current stage
PRN 1008	**Bruton's Tyrosine Kinase (BTK) inhibitor** Inhibits B cell activation and antibody induction.	**Phase III** **STOPPED for pemphigus**
Ianalumab/VAY736	**Fully human antibody against BAFF-R (B-cell activation factor receptor)** Depletes peripheral B-cells 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** **ONGOING**
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**
TPM203	Nano-particle based therapeutic for **T-reg stimulation**	**Phase I**

PC111: Positioning in Pemphigus



PC111 Target Population is estimated as >35% of current pemphigus patients

PC111 in SJS/TEN

STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS[7]

- Rare toxic dermatosis associated with several drug classes or infections
- Destruction and detachment of skin and mucous membranes:
  - SJS: <10% BSA
  - SJS/TEN: 10-29% BSA
  - TEN: >30% BSA
- Acute and often life-threatening
- Market size (2030) >8B$ growing at a CAGR of 4%[8]

EPIDEMIOLOGY[7,8,9]

- Incidence
  - 1/319,000 in EU
  - 1-2/1,000,000 globally
- **Estimated Global Addressable Market: 5,000-10,000 patients**
- Onset at any age, with risk increase by middle age
- Mortality: up to 30% in in patients with extensive form, sequelae in >80% of patients

UNMET MEDICAL NEED[8,9]

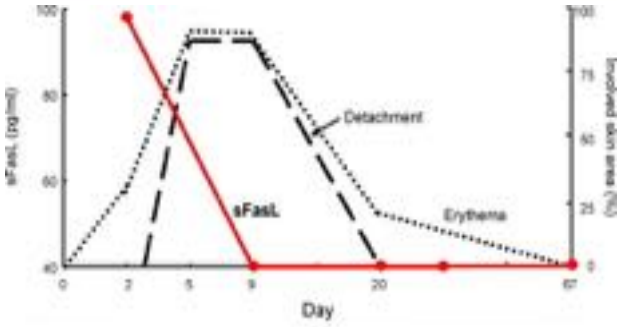
- No approved treatment
- Use of high-dose immunoglobulins of limited efficacy
- ICU/burn unit care setting needed

Treatment goals

- Improve survival rate of severe form
- Prevent less severe form progression or sequelae

References - 7) Orphanet (Mar 2023); 8) Data Bridge Market Research (2022); 9) UpToDate (Wolters Kluwer, Mar 2023)

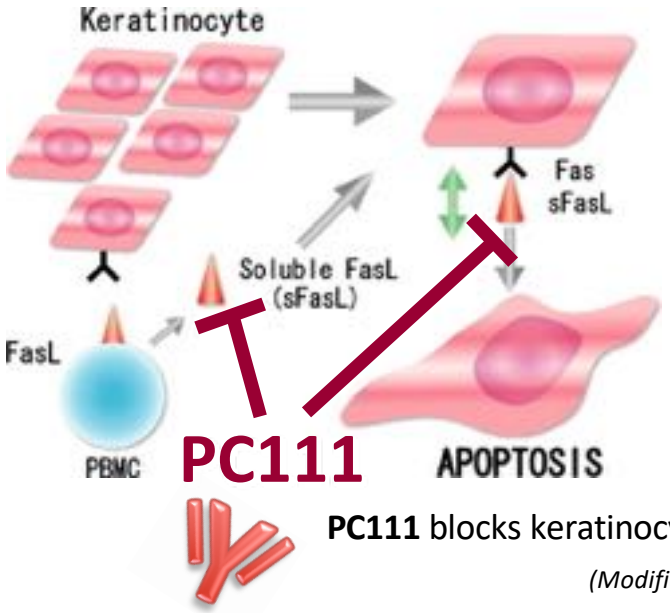
The Target (FasL): Validation in SJS/TEN



- 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**



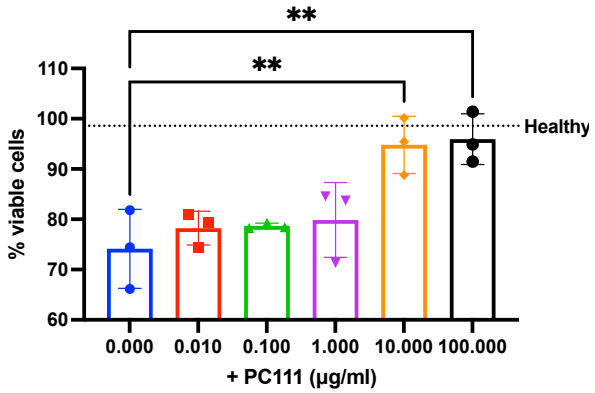
PC111 blocks keratinocyte apoptosis

(Modified from Abe R. at al, 2008)

PC111: Evidence in SJS/TEN

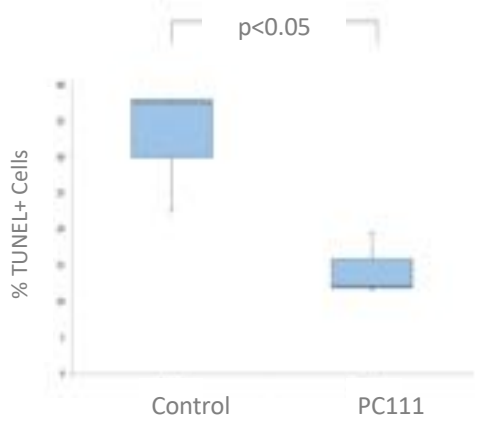
In-vitro Study (Prof. R. Abe) NIIGATA UNIVERSITY

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



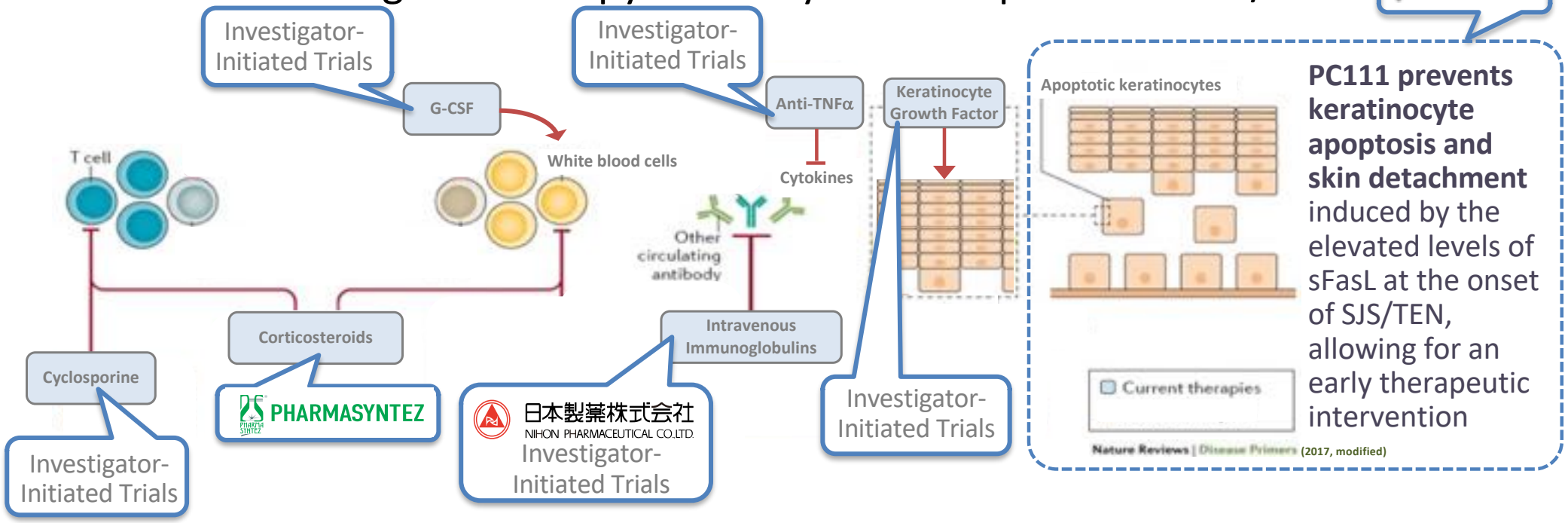
In-vivo Study (Prof. R. Abe)

- **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



PC111: Highly Differentiated Asset

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



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

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

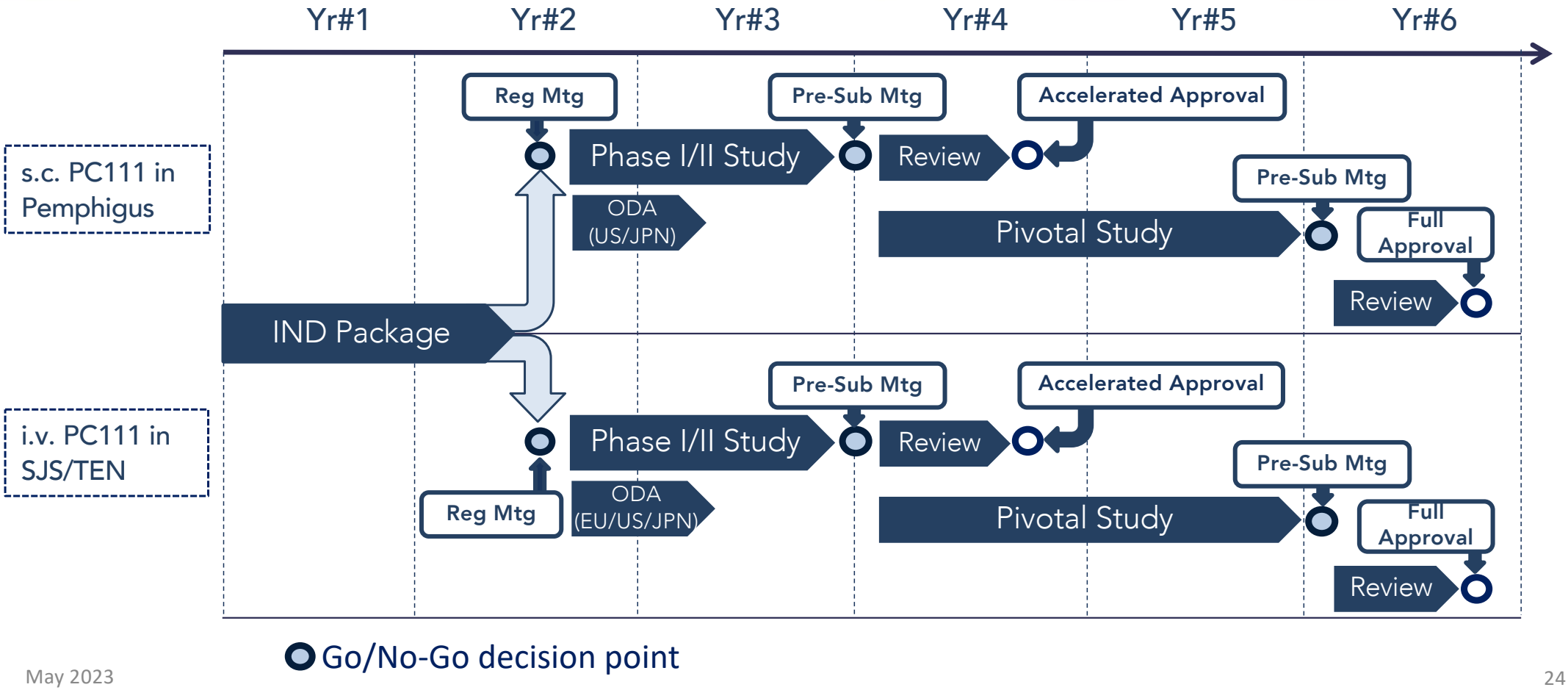
PC111: a significant step forward

- 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 in Dermatology

Orphan skin diseases where **sFasL targeting** by PC111 can be beneficial

Disease	Epidemiology	Rationale
Drug-induced hypersensitivity syndrome (DIHS)[12]	• Annual 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)[13]	• 0.1-1.0/1,000 drug exposures (anticonvulsants) • 10% mortality rate, most commonly from fulminant hepatitis	• High sFasL levels in patients sera correlating with disease severity
Erosive Oral and Genital Lichen Planus[14] predisposing to Squamous Cell Carcinoma	• Prevalence varies from 0.5-2.6% (oral) to 0.1-1.7% (vulvar) worldwide	• High sFasL levels in patients sera

References - 12) Hama N, J Allergy and Clin Immunol Pract 2022 ; 13) Yang F, Eur J Dermatol 2018; 14) Didona D, Front Immunol 2022

Additional Indications for PC111

Non-dermatological diseases where **sFasL targeting** by PC111 can be beneficial

Disease	Epidemiology	Rationale
Acute Respiratory Distress Syndrome[15]	• Annual incidence: 3 million cases/year worldwide • Functional limitations and cognitive impairment in half of survivors • Mortality rate up to 40%%,	• High sFasL levels in bronchial lavage, plasma and lung tissue • Correlation between sFasL levels and mortality
Rheumatoid Arthritis[16]	• 1% general population worldwide • Mortality rate not increased	• High sFasL levels in joints and synovial fluids • sFasL is pro-inflammatory in RA • sFasL stimulates synoviocyte proliferation
Systemic Lupus Erythematosus[17]	• Incidence and newly diagnosed: 5/100.000 persons/year • Mortality rate of 22.2 and 14.8 per 1000 person-years	• sFasL levels are markedly increased in SLE patients • High sFasL associates with renal SLE and active disease
Sjogren syndrome[18]	• Incidence: 0.5-1% general population • Mortality rate not increased	• High sFasL levels in in saliva and sera • No correlation with disease severity

References - 15) Martin TR, Proc Am Thorac Soc 2005; 16) Kim WU, Arthritis Res Ther 2006; 17) Vincent FB, BMJ 2020; 18) Vincent FB, Clin Exp Rheumatol 2019

Intellectual Property, Market 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**
  - US Application no. 63/454,453 (filed 03/2023, 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)

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 for a **partner** to exploit PC111 potential in pemphigus and SJS/TEN
  - Capital raise or asset acquisition

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