Development of a systemic lupus erythematosus (SLE) QSP model linking systemic biomarkers to cutaneous clinical score (CLASI) outcomes.

Vincent Hurez[1]*, Krishnakant Dasika[1], Katherine Kudrycki[1], Robert Sheehan[1], Christina Friedrich[1], Mike Reed[1], Glenn Gauderat[2], Audrey Aussy[2], Loubna Chadli[2], Florian Chassereau[2], Sylvain Fouliard[2], Sandra Hubert[2], Emiko Desvaux[2], Perrine Soret[2], Alexia Blesius[2], Philippe Moingeon[2]. [1] *Rosa and Co. LLC, San Carlos, CA, USA;* [2] *Servier, Suresnes, France,* *vhurez@rosaandco.com

Introduction

Background

- **QSP models** must find a way to integrate biological components to **predict the clinical endpoints of interest to the clinical team**
- **SLE is particularly challenging** even for clinicians designing new clinical trials due to the variety of clinical manifestations and the choice between multiple clinical scores
- QSP modeling allows to **link mechanistic pathways to SLE clinical score** components and support rational trials designs with predictions of relevant clinical SLE endpoints

Objectives

- Establish a link between systemic pathways involved in cutaneous SLE pathophysiology represented in the QSP model and components of the clinical SLE activity scores
- Calibrate the change in the SLE disease activity score components using published response to standard of care (SOC) therapies
- Qualify the overall SLE disease activity endpoints and evaluate clinical responses to SOC therapies and new SLE drugs

SLE Model Design

- The SLE QSP Platform includes **prototypic lymph node (LN), skin and blood compartments** with relevant **cell types and functions (Fig. 1)**:
  - **Immune cells:** pDCs, T cells, B cells, macrophages
  - **Skin cells:** keratinocytes (KCs) and corneocytes
  - Cell proliferation, differentiation, mediators and autoantibodies (auto-Abs) production (blue arrows)
  - Positive (green) and negative (red) regulation by pro- and anti-inflammatory mediators and recruitment by chemokines
- The model also includes **steroids** as SOC therapies and **anifrolumab** anti-IFNα receptor (IFNAR) as a test SLE therapy. The primary endpoint is Cutaneous Lupus Area and Severity Index (**CLASI**).

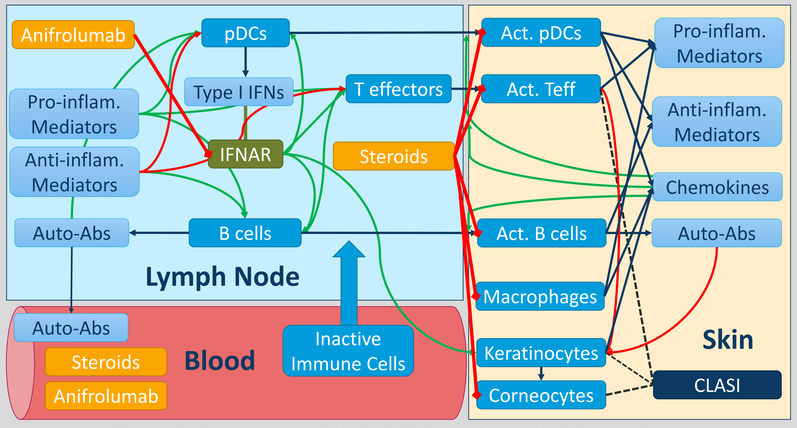

Figure 1: Components of the SLE QSP model and their interactions.

Cutaneous Lupus and CLASI Score

Cutaneous SLE Lesions Characteristics

- Increased KC activity and differentiation induced by inflammatory mediators resulting in **rapid skin turnover (Fig. 2)**
- Altered corneocyte layer organization resulting in **"scaling"** aspect
- Increased vascular permeability resulting in redness or "**erythema**"
- Immune cell infiltration and auto-Abs deposit at the basal lamina propria with basal KC, melanocyte and hair follicle cell death
  - Can ultimately result in **mucosal membrane ulcers, hair loss or alopecia, skin dyspigmentation and scarring**

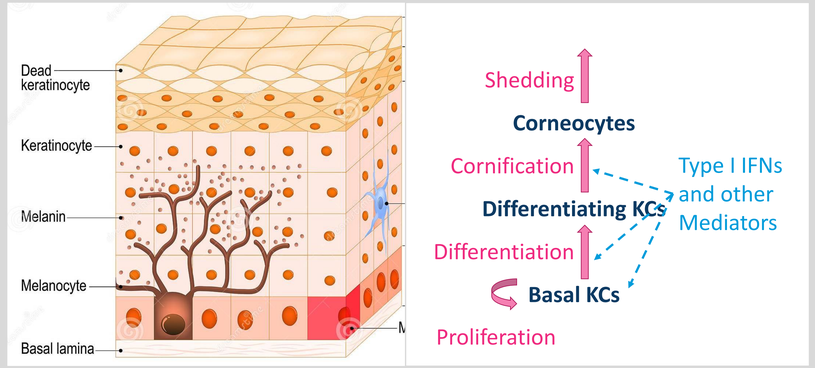

Figure 2 : Structure of the epidermis (left) and KC lifecycle representation (right).

CLASI Score Implementation

- Individual CLASI subscores were linked to relevant model biological components based on scientific understanding of the **mechanisms involved for each clinical manifestation (Fig. 3)**
- A baseline average value was estimated for each subscore*
- A mathematical dynamic relationship was established between model components and individual CLASI subscores

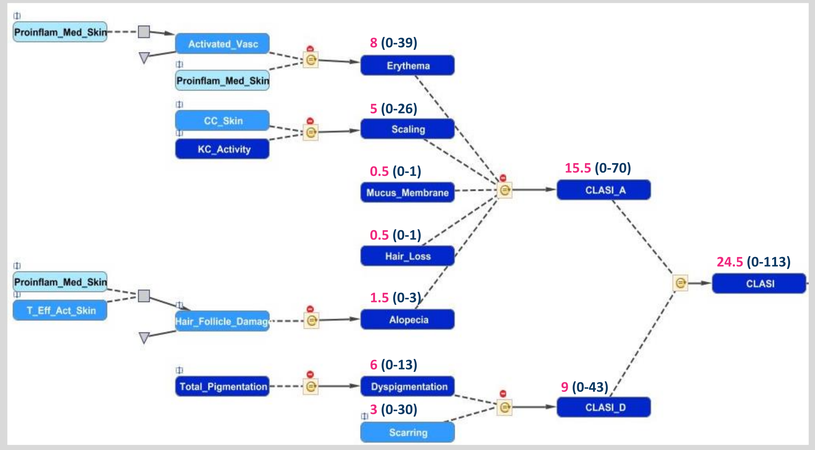

Figure 3: CLASI subscores in the Platform with **baseline values*** and (**maximum clinical range**).

* Baseline values for each CLASI subscore estimated from literature data in moderate SLE patients (AIE'ed et al. 2018)

CLASI-A Response to Therapies

Steroid Effects Implemented

Table I: Steroid effects on various cell types based on in vitro literature data

Cell Type	IC50 (steroids)	Range of in vitro inhibition	References
Keratinocytes	10-100 nM 30 nM 30 nM	-20-70% activation -10-40% proliferation -60-80% apoptosis	(Stojadinovic et al. 2007, Le et al. 2010, Guichard et al. 2015, Zulfakar, Ong, and Heard 2012, Trautmann et al. 2001)
DCs	5-50 nM	-50-80% activation	(de Jong et al. 1999, Piemonti et al. 1999, Weichhart et al. 2011, Shodell, Shah, and Siegal 2003)
T cells	1-10 nM	-60-90% activation	(Migliorati et al. 1994, Braun et al. 1997, Sun et al. 2011)
B cells	10-100 nM	-25-70% activation	(Tseng et al. 2006, Weisbart and Colburn 1984, Chaia-Semerena et al. 2020, Cupps et al. 1985, Bowen and Fauci 1984)
Macrophages	1-10 nM	-60-90% activation	(Lim et al. 2007, Werb 1978, Luedke and Cerami 1990)
Vasculature	30 nM	-50-70% activation	(Logie et al. 2010)

- Steroid response was calibrated to match placebo CLASI-A response from recent anifrolumab clinical trial (Bruce et al. 2019) (not shown)

Anifrolumab + SOC background steroid simulations match clinical trial CLASI-A response in SLE patients.

- Anifrolumab Q2W SC was simulated on a steroid background therapy and compared to recent clinical trial results (Bruce et al. 2019) (**Fig. 4**)

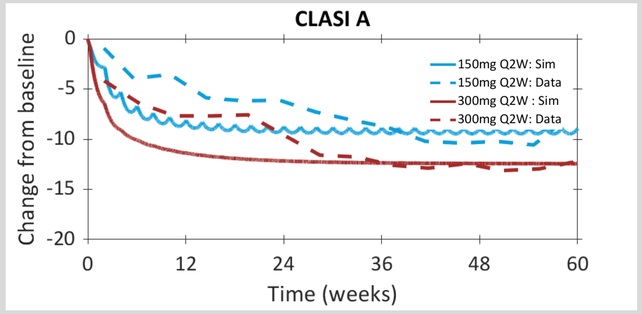

Figure 4: Model simulations (solid lines) match clinical data (dashed lines) for reduction in CLASI-A score in SLE patients treated with 150 mg or 300 mg anifrolumab Q2W SC.

Conclusions

- The **SLE QSP Platform** can predict CLASI scores relevant to **clinical endpoint measured in SLE trials**
- The model helped established mechanistic **relationships between biological entities and clinical manifestations** that could provide useful **biomarkers**
- Calibration of the QSP model CLASI could be improved with **better reporting of CLASI subscores in SLE trials**

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For more information about this work, please contact:
Vincent Hurez
Rosa & Co LLC
vhurez@rosaandco.com