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Inhibition of Interleukin-2-Inducible T Cell Kinase with Soquelitinib demonstrates efficacy in preventing lung damage in murine models of systemic sclerosis

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Introduction

- **Systemic sclerosis (SSc)** is a rare autoimmune disease marked by vascular damage and fibrosis, with interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) being major causes of morbidity and mortality (1).
- **T cell dysregulation**, especially **Th2 and Th17** polarization, is key in SSc pathogenesis, driving chronic inflammation and fibrosis through cytokines like IL-4, IL-13, and IL-17 (2).
- In the **Fra2** transgenic mouse model, overexpression of the AP-1 transcription factor Fra2 triggers spontaneous inflammation and fibrosis through upregulation of Th2 and Th17 pathways and reduced Treg activity in the lungs and skin, resembling SSc (3).
- **Soquelitinib (SQL)**, a selective ITK inhibitor, targets Th2 and Th17 pathways, showing potential in SSc by reducing lung inflammation and fibrosis in experimental models. It is in clinical trials for atopic dermatitis and T-cell lymphoma (4).

Objective

To evaluate the effects of SQL in two murine models of SSc-associated lung disease: ILD and PAH

Methods

- **Animals:** Female C57BL/6 mice (bleomycin model) were housed at Charles River Laboratories, USA, and Fra-2TG mice at the Cochin Institute, Paris. Animal experiments followed ethical guidelines approved by Université Paris Cité.
- **Soquelitinib Treatment:** SQL was administered via oral gavage, with a mouse chow formulation developed for chronic dosing.

Two SSc Animal Models:

1. **Bleomycin Model:** Thirty-four C57BL/6 mice received bleomycin (1.5 U/kg) or saline. SQL or vehicle treatment began on day 7 and continued until day 21.
2. **Fra-2 transgenic Mice:** Fra-2 mice were split into four groups, treated with SQL chow starting at 11 weeks.

- **Clinical Follow-Up:** Mice were monitored weekly, with clinical scores (0-10) based on weight loss and symptoms.
- **Histopathology:** Lung tissue was stained for analysis.
- **Hemodynamic Assessments:** RVSP was measured in unventilated mice for hemodynamic analysis.

Results

1. Soquelitinib improves clinical scores and alleviates lung fibrosis in Fra-2 mice

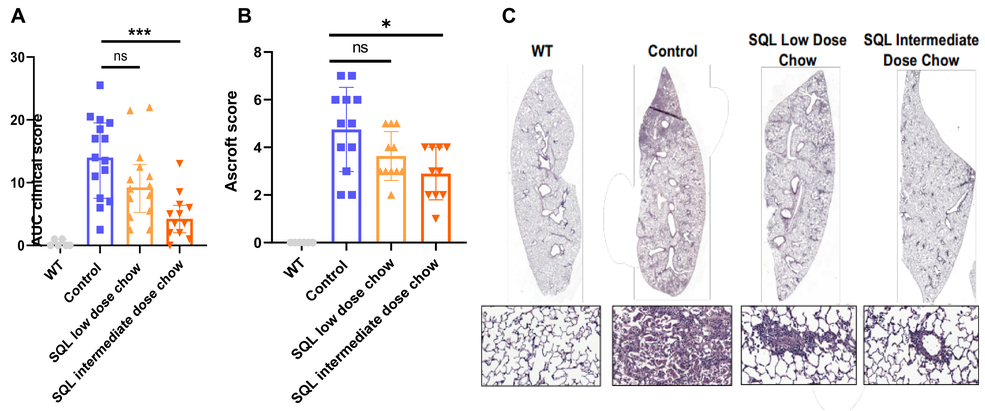

Figure 1. (A) The clinical improvement for the high dose treated mice as determined by the area under the curve (AUC) was significant. (B) The Ashcroft score is improved by SQL intermediate dose and as illustrated by the representative histology (C). * p<0.05, *** p<0.001.

2. Soquelitinib reverses pulmonary hypertension in Fra-2 mice

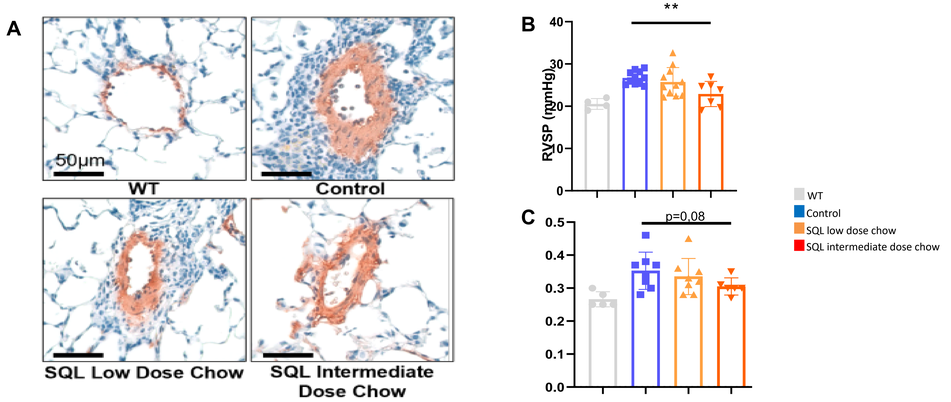

Figure 2. (A) Histology images of the remodeling of the vessels assessed by staining for smooth muscle actin. (B) The right ventricular systolic pressure (RVSP) was lowered by SQL treatment at the intermediate dose. (C) Trend toward an improvement of the Fulton index (right ventricular weight divided by the combined weight of the left ventricle and the intraventricular septum) in Fra-2 mice treated with SQL intermediate dose (p=0.08). Each dot in a bar graph represents one mouse. WT=wild type. ** p<0.01.

3. Soquelitinib alleviates lung fibrosis and reduces mRNA associated with fibrosis in bleomycin-lung fibrosis induced mice

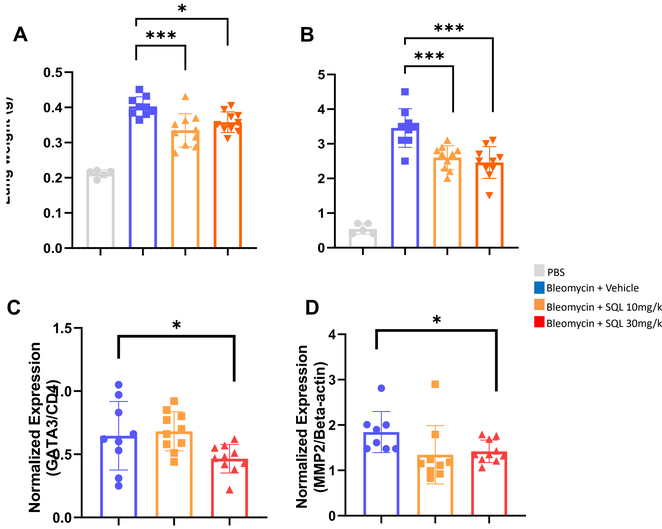

Figure 3. (A) Absolute lung weight among different groups is shown. (B) SQL significantly decreased lung structural damage. Modified Ashcroft scores for the severity of fibrosis are shown. (C) Expression of the Th2 lineage defining transcription factor, GATA3. (D) Fibrosis-associated transcripts of MMP2 in lung tissues were determined by quantitative RT-PCR. Each dot in a bar graph represents one mouse. p<0.05; *** p<0.001.

Conclusions

1. **Soquelitinib (SQL), a selective ITK inhibitor, reduced lung damage in two SSc mouse models.**
2. **In the bleomycin model, SQL decreased leucocyte infiltration and attenuated interstitial lung damage. In Fra-2 mice, SQL improved clinical scores, reduced interstitial lung damage, vascular remodeling, and signs of PAH.**
3. **These results support further clinical evaluation of SQL as a potential immunomodulatory therapy in SSc.**

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