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Pharmaceutical Blockade of the Neonatal Fc Gamma Receptor Ameliorates Autoimmunity, Inflammation, and Fibrosis in the Topoisomerase I Mouse Model of Systemic Sclerosis

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BACKGROUND | METHODS

Systemic sclerosis (SSc) is a systemic fibrosing orphan disease associated with high morbidity and increased mortality.[1,2] The hallmark of the disease is accumulation of extracellular matrix proteins by pathologically activated fibroblasts.[2] Therapeutic approaches to inhibit the aberrant release of extracellular matrix in SSc are available only for pulmonary fibrosis, and these approaches are rather ameliorating fibrotic remodeling, but are in most patients not able to stop progression.[1] No therapies are approved for other fibrotic manifestations of SSc, and true disease-modifying pharmacologic approaches are not available. Thus, there is a great medical need for improved therapies.

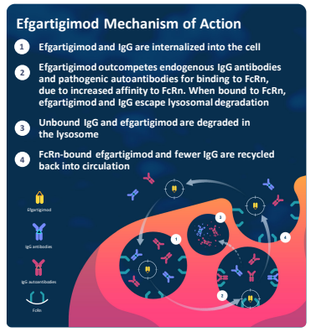


TABLE 1 Characteristics of Topo I Mouse Model

Topoisomerase I Immunization Mouse Model	
Pathogenic pathways covered by Topo I model	
• Inflammation	• Type-I IFN upregulation
• Skin and lung fibrosis	• Long-term treatment of chronic disease (8-weeks model)
• Autoantibodies	
Treatment: FcRn antagonist (20 mg/kg)	
Assessments of inflammatory/fibrotic changes by:	
• Skin thickening and immune cell infiltration	• Quantification of HYP in skin/lungs
• Collagen deposits in lungs	• Myofibroblast numbers
• Fibrotic changes in lungs	• Bulk RNAseq in skin
	• Cytokines

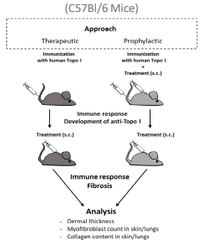
Here, we evaluated the effects of treatment with FcRn antagonist, molecule reducing autoantibody and IgG levels in the mouse model of topoisomerase-induced fibrosis (**Table 1**).

Dermal fibrosis was induced in 5-week-old C57Bl/6 mice by biweekly SC immunizations with recombinant DNA topoisomerase I mixed with CFA (Topo I immunization) or only CFA (no immunization).[3,4] Animals were also treated twice weekly with PBS or FcRn antagonist in prophylactic or therapeutic approach (**Figure 1**), or daily with nintedanib. All studies were performed according to the EU animal welfare standard. The study has been approved by the local animal welfare committee.

Analyses of skin or/and lung tissues for collagen, fibrotic changes in skin and lungs, as well skin thickening and myofibroblast counts were performed after 8 weeks by immuno-histologic staining with Sirius red, trichrome, H&E or anti-αSMA staining, respectively. Histological changes of pulmonary fibrosis were quantified by Ashcroft Scoring 5. HYP in skin was measured by biochemical assay. Bulk RNAseq was performed on skin samples. Cytokine levels were measured by Olink analysis.

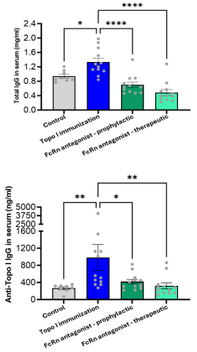
All data are presented as mean ± SEM. Statistical significance performed by using one-way ANOVA. *P* values are expressed as follows: 0.05 > *P* > 0.01 as *; 0.01 > *P* > 0.001 as **; *P* < 0.001 as ***; *P* < 0.0001 as ****.

FIGURE 1 Treatment of Topo I Immunized Mice



RESULTS

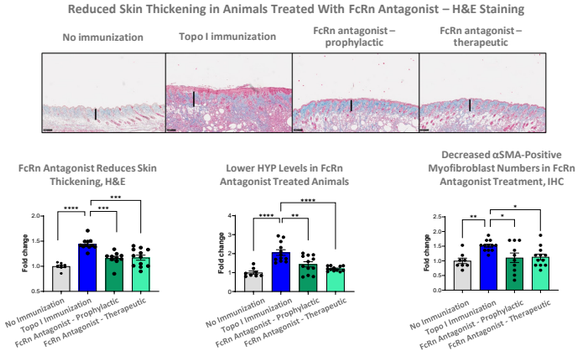
FIGURE 2 FcRn Antagonist Reduces ATA Levels



*0.05 > *P* > 0.01, **0.01 > *P* > 0.001, **** *P* < 0.0001

FcRn antagonist reduces IgG and anti-Scl70 levels in peripheral blood

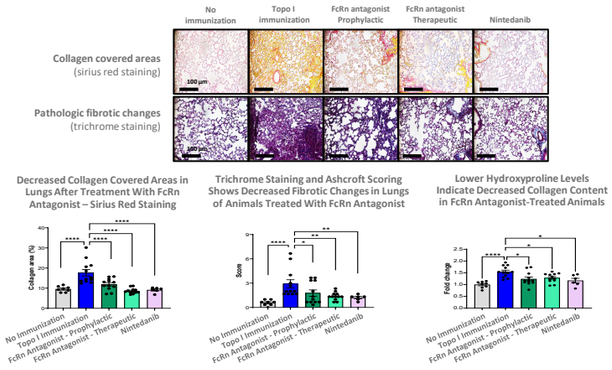
FIGURE 3 FcRn Antagonist Ameliorates ATA-Dependent Dermal Fibrosis in Mice



*0.05 > *P* > 0.01, **0.01 > *P* > 0.001, ***P < 0.001 , **** *P* < 0.0001

FcRn antagonist reduces ATA dependent skin thickening. The treatment with FcRn antagonist causes potent antifibrotic effects with significant decrease in dermal thickening, decreased HYP levels and less myofibroblast differentiation compared to vehicle-treated mice

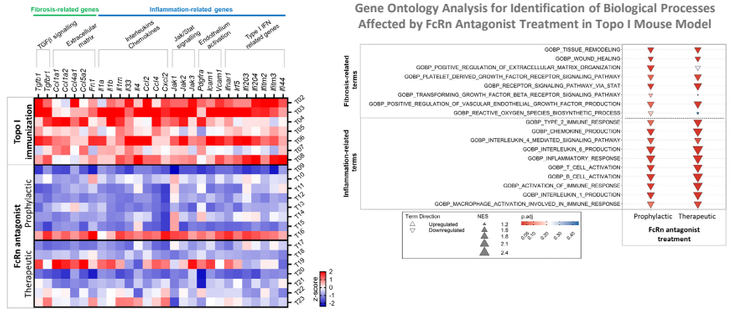
FIGURE 4 FcRn Antagonist Ameliorates ATA-Dependent Lung Fibrosis in Mice



*0.05 > *P* > 0.01, **0.01 > *P* > 0.001, ***P < 0.001 , **** *P* < 0.0001

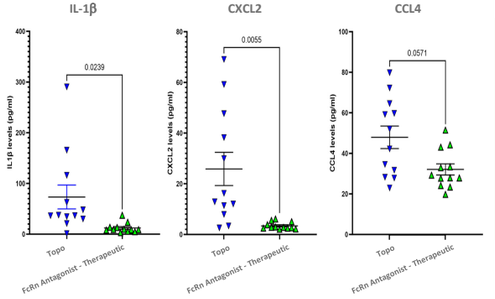
Antifibrotic effects of FcRn antagonist are also observed on pulmonary fibrosis. The collagen covered area in lung parenchyma, Ashcroft scores, and hydroxyproline content were significantly reduced as compared to vehicle-treated mice. The antifibrotic effects of FcRn antagonist were comparable to those of nintedanib

FIGURE 5 FcRn Antagonist Reduces Expression of Inflammation and Fibrosis-Related Genes in the Skin of ATA-Producing Mice



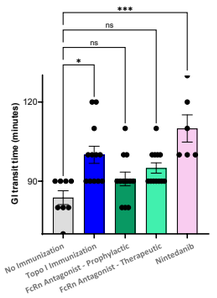
Expression of fibrosis- and inflammation-related genes significantly downregulated in the skin of mice treated with FcRn antagonist. Several genes involved in fibrosis, e.g, TGFβ signaling and ECM genes, as well as genes involved in inflammation (chemokines, interleukins, JAK kinases, endothelium activation molecules, and type I IFN signaling) downregulated by FcRn antagonist treatment. Gene ontology analysis confirms significant gene expression reduction in genes related to inflammation and fibrotic process

FIGURE 6 FcRn Antagonist Treatment Decreases Systemic Levels of Profibrotic Cytokines/Chemokines



FcRn antagonist reduces systemic levels of IL1β (important proinflammatory and profibrotic cytokine in SSc), CXCL2 (key immune cell attractant involved in wound healing, angiogenesis, and pulmonary fibrosis) and CCL4/MIP1β (leukocyte attractant with involvement in pulmonary fibrosis)

FIGURE 7 FcRn May Improve ATA-Related GI Defect



*0.05 > *P* > 0.01, ***P < 0.001

FcRn antagonist partially reduces ATA-related GI transit delay

KEY TAKEAWAYS

Topo I immunized mice show severe lung and skin fibrosis with induction of IgG autoantibodies

Treatment with FcRn antagonist reduces skin thickening, myofibroblast numbers, and collagen levels in skin as well as reduces collagen levels, hydroxyproline levels, and pathogenic fibrotic changes in lungs. In addition, treatment with FcRn blocker partially reduced GI transit delay

Reducing IgG and autoantibody levels significantly affects expression of genes involved in fibrosis and inflammation as well as significantly decreases levels of circulating profibrotic cytokines

Targeting IgG autoantibodies significantly reduces pathologic changes in Topo mouse model, which indicates disease causative and pathogenic properties of anti-Scl70 autoantibodies

These findings highlight that, in a murine model of SSc, FcRn blockade may have potential to simultaneously target the autoimmune, inflammatory and fibrotic features of SSc and highlight the potential of autoantibody-reducing therapies as disease-modifying approaches in this disease

A randomized, controlled phase 2 trial with FcRn antagonist, efgartigimod, in SSc is currently ongoing

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ABBREVIATIONS

ATA, autoantibodies to topoisomerase I; **CFA**, complete Freund's adjuvant; **EU**, European; **FcRn**, neonatal Fc receptor; **GI**, gastrointestinal; **H&E**, hematoxylin and eosin stain; **HYP**, hydroxyproline; **IFN**, interferon; **IgG**, immunoglobulin G; **IHC**, immunohistochemistry; **JAK**, Janus kinase; **PBS**, phosphate-buffered saline; **SC**, subcutaneous; **SEM**, standard error of the mean; **SSc**, systemic sclerosis.

DISCLOSURES AND ACKNOWLEDGMENTS

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