

Supplemental Table 1. Histopathological observations in tissues of male NOD mice after 12 weeks of treatment with eye drops containing Rapa in PEG-DSPE vs. vehicle alone

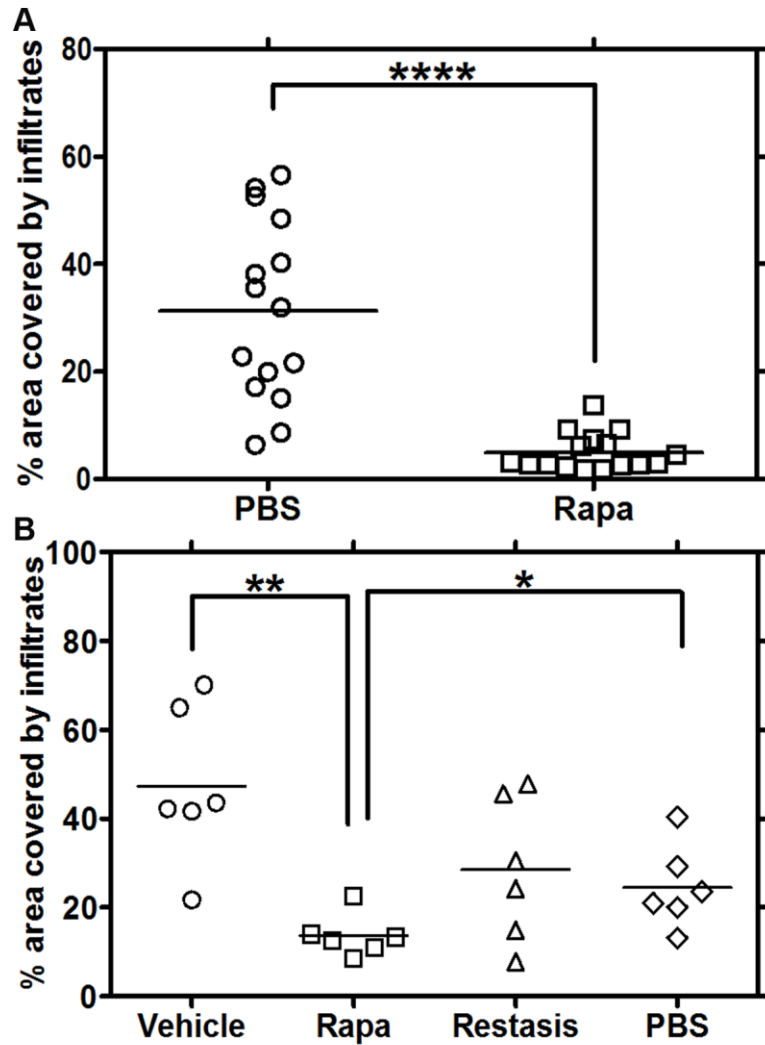
Organ	Vehicle treated (n=5)	Rapa treated (n=5)
Kidney	H&E stained sections displayed kidney with a well-defined cortex and medulla. Numerous glomeruli were identified in the cortex. The renal medulla with loops of Henle and collecting ducts of Bellini were identified. No histopathologic abnormality was identified in the kidney.	H&E stained sections displayed kidney with a well-defined cortex and medulla. Numerous glomeruli were identified in the cortex. The renal medulla with loops of Henle and collecting ducts of Bellini were identified. No histopathologic abnormality was identified in the kidney.
Lung	The H&E stained sections displayed lung parenchyma with alveolar ducts, alveolar sacs, terminal and respiratory bronchioles. Occasional alveolar macrophages were noted. In two of these 5 mice, mild interstitial pneumonitis was present; however, the pathologic changes were nonspecific and in an appropriate setting, best fit with changes seen in early Sjögren's syndrome.	The H&E stained sections displayed lung parenchyma with alveolar ducts, alveolar sacs, terminal and respiratory bronchioles. Occasional alveolar macrophages were noted. There was no evidence of inflammation, fibrosis, atelectasis or emphysematous changes. No histopathologic abnormalities were identified in the lung but in one of these 5 mice, mild focal chronic inflammation, interstitial pneumonitis and congestion were identified; however, the changes were nonspecific and in an appropriate setting, best fit with changes seen in early

		Sjögren's syndrome.
Liver	The H&E sections displayed liver parenchyma with hepatocytes and sinusoids with Kupffer cells. Several hepatocytes were binucleated. Portal triads with bile duct, hepatic artery and portal vein were identified and were essentially unremarkable. Focal mild chronic inflammation was noted in one of these mice but the change, in an appropriate setting, best fits with changes seen in early Sjögren's syndrome.	The H&E sections displayed liver parenchyma with hepatocytes and sinusoids with Kupffer cells. Several hepatocytes were binucleated. Portal triads with bile duct, hepatic artery and portal vein were identified and were essentially unremarkable. No histopathologic abnormality was identified in the liver.

Supplemental Fig. 1. Comparison of Rapa eye drops and Restasis® in reducing

LG inflammation relative to controls. A) Male NOD mice aged 8 weeks were treated with Rapa eye drops or PBS twice daily for 12 weeks. Lymphocytic infiltration was significantly decreased in LG from Rapa-treated mice (n=15) relative to PBS-treated mice (n=16). Image analysis of H&E stained LG sections allowed the calculation of % area with lymphocytic infiltrates relative to the entire LG section. **** indicates p<0.0001. **B)** A second 12-week eye drop study was carried out, initiated in male NOD mice aged 8 weeks, to compare Rapa eye drops to Restasis®, PBS, and the vehicle for Rapa, PEG-DSPE. Image analysis of H&E stained LG sections allowed the calculation

of % area with lymphocytic infiltrates relative to the entire LG section. Rapa eye drops were significantly more effective than PBS (*p=0.05) or vehicle (**p=0.009) in reducing the extent of LG lymphocytic infiltration, while Restasis® showed no significant change. n=6 in each group. Crossbar represents the mean.



Supplemental Fig. 2. Analysis of conjunctival inflammation and quantification of goblet cell density.

A) Representative histology images of mouse conjunctivas from male NOD mice after treatment with eye drops containing Rapa in PEG-DSPE or vehicle alone for 12 weeks twice daily. The tissue was paraffin embedded, and 5 serial sections from three non-consecutive slides were stained with periodic acid-Schiff's stain and Alcian Blue. **B)** There was no significant difference between the goblet cell density between the vehicle (n=14) and drug (n=13) treatment groups (p=0.1572).

