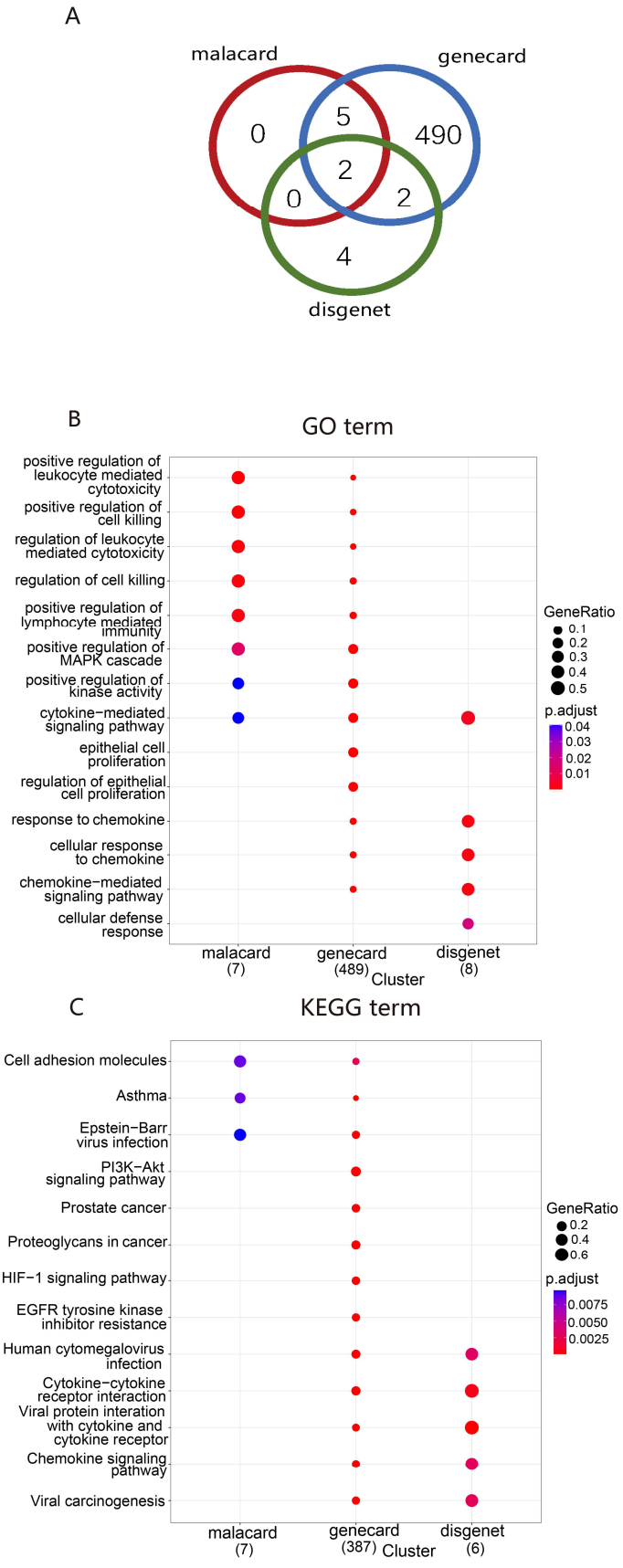
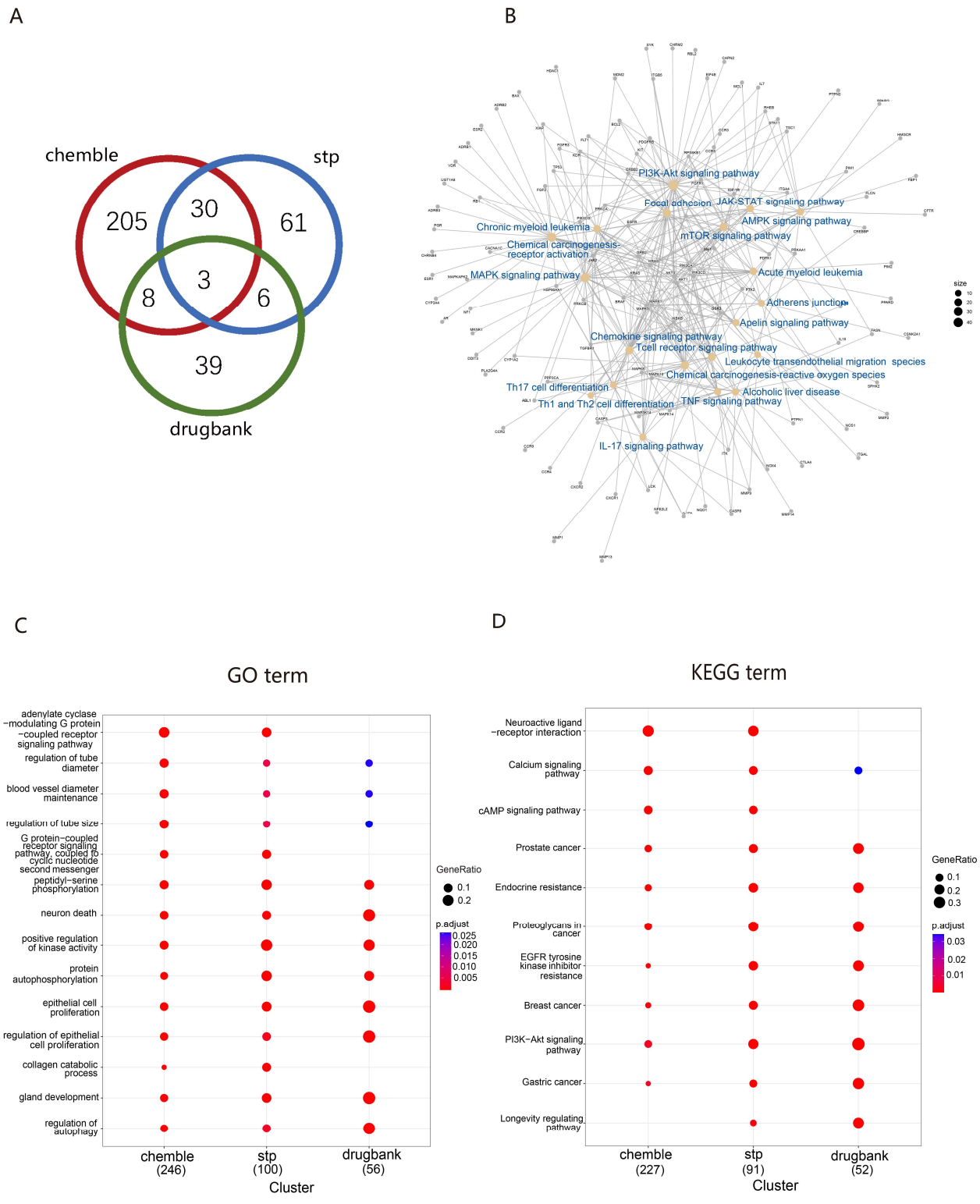
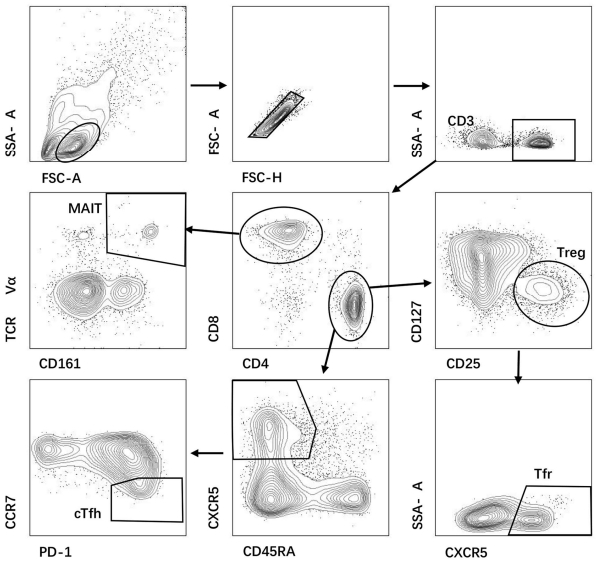


Supplemental Figure 1. Pathology pathway enrichments for RPF. (A) Overlap of genes queried from the three gene-disease databases; (B) Gene Ontology (GO) enrichment for the identified genes in each database; (C) Pathway enrichment using Kyoto Encyclopedia of Genes and Genomes (KEGG) database for the identified genes in each database.

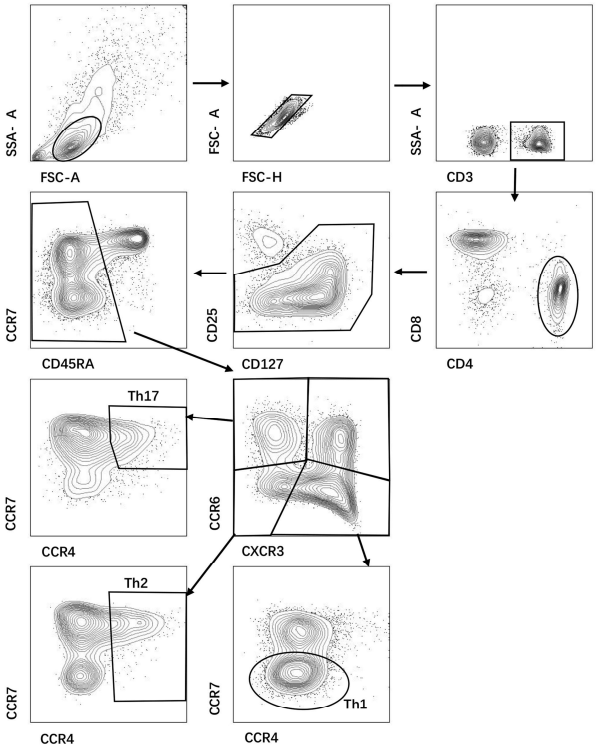


Supplemental Figure 2. Target genes and pathways of sirolimus. (A) Overlap of genes queried by sirolimus from the three drug-gene databases; (B) signaling pathway network enriched from genes affected by sirolimus. (C) GO enrichment for the identified genes in each database; (D) Pathway enrichment using KEGG database for the identified genes in each database.

A



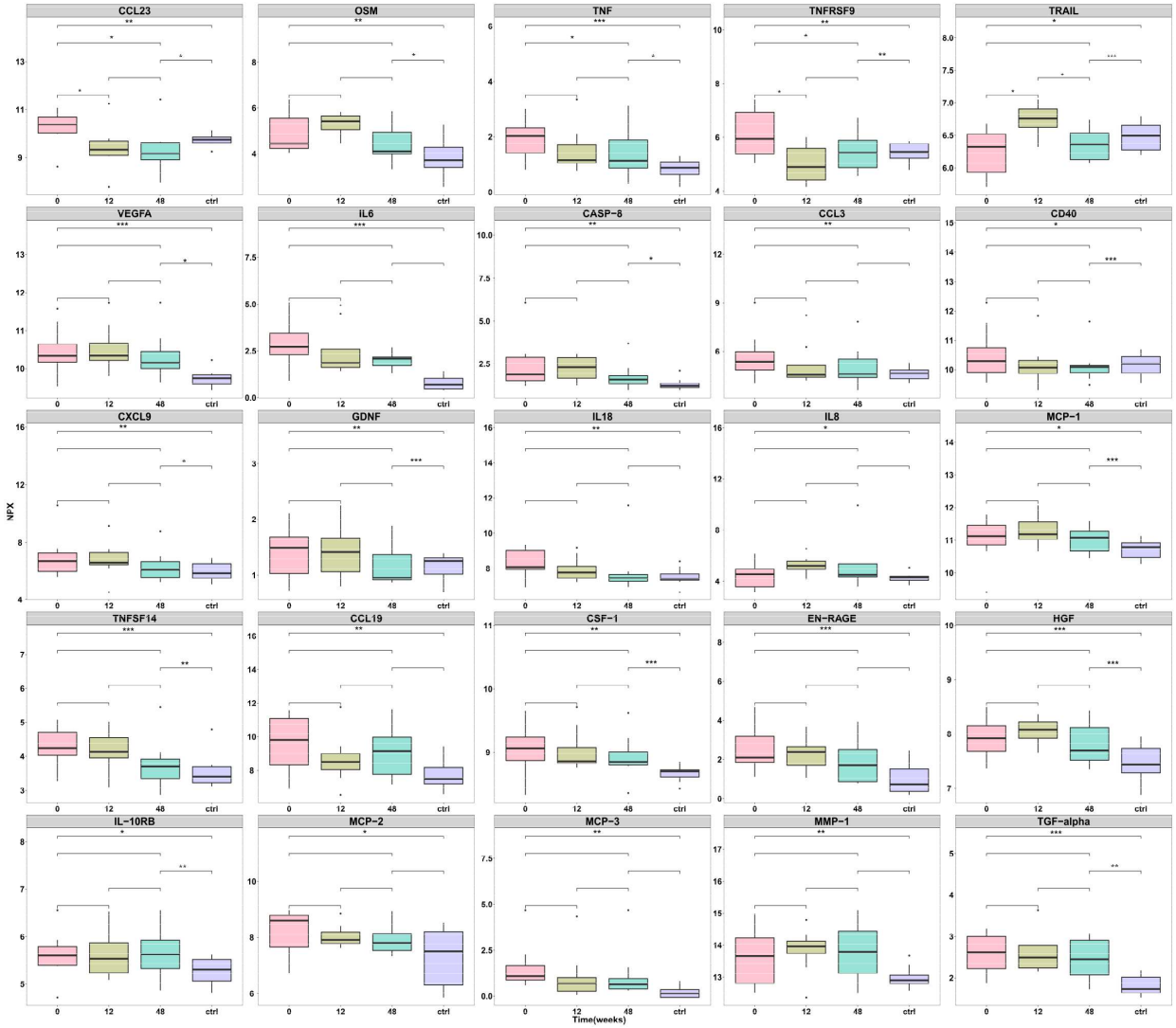
B



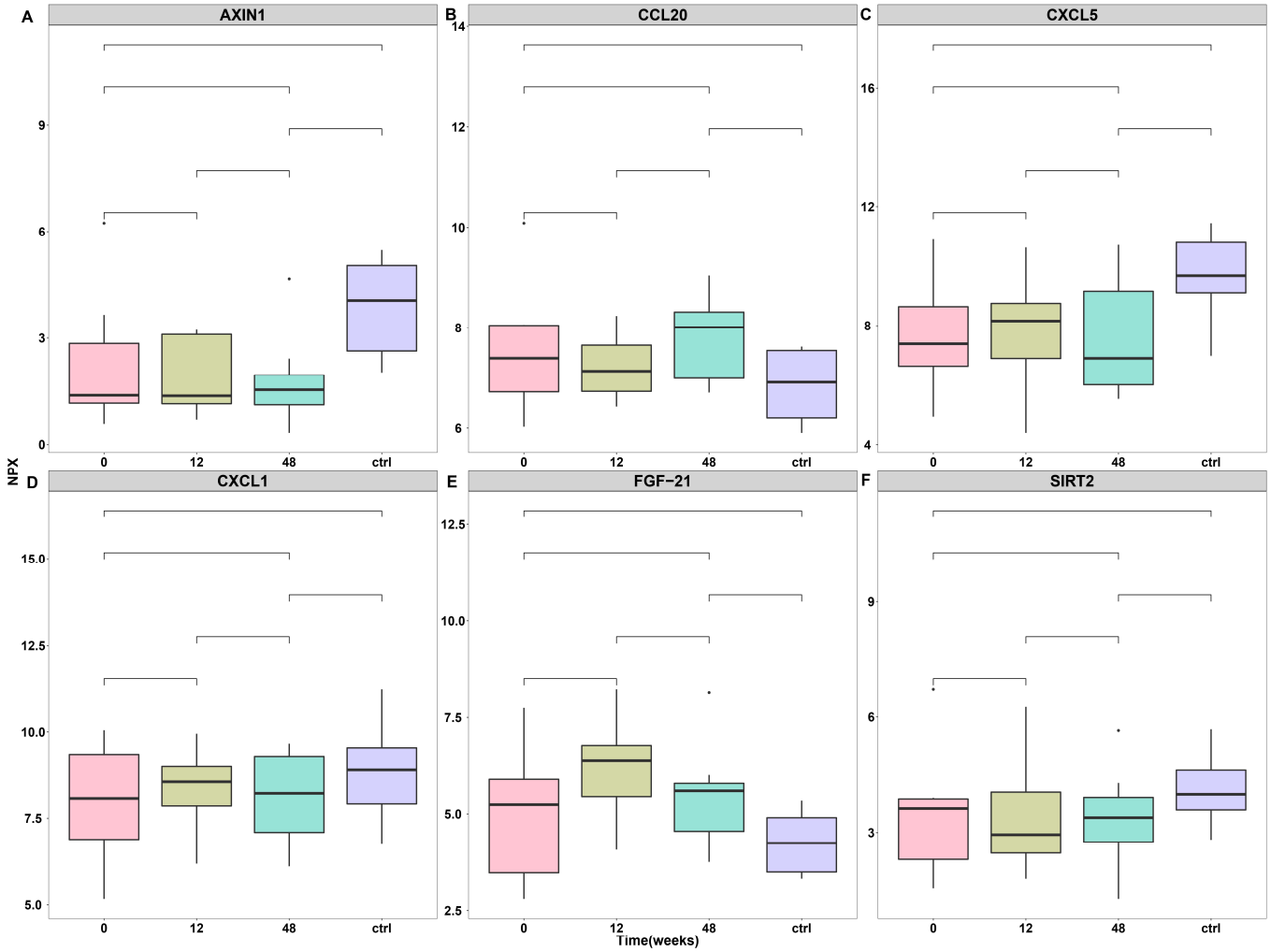
C

T_H1	$CD3^+CD4^+$ $CD8^-CXCR3^+CCR6^-CCR4^-CCR7^{low}$
T_H2	$CD3^+CD4^+CD8^-CXCR3^+CCR6^-CCR4^+CCR7^{low}$
T_H17	$CD3^+CD4^+CD8^-CXCR3^-CCR6^+CCR4^+CCR7^{low}$
T_{REG}	$CD3^+CD4^+$ $CD8^-CD25^{high}CD127^{low}$
MAIT	$CD3^+CD4^-CD8^+TCRV\alpha^+CD161^{high}$
cT_{FH}	$CD3^+CD4^+CD8^-CD45RA^-CXCR5^+CCR7^{low}PD\text{-}1^{high}$
T_{FR}	$CD3^+CD4^+CD8^-CD25^{high}CD127^{low}CXCR5^+$

Supplemental Figure 3. Phenotypic characterization of T-cell subsets by Flow cytometry.Illustrative examples of the lymzphocyte gating strategy were provided for identifying T cell subset (A) T_{FR} and (B) T_H1; (C) a complete marker list for each T cell subset. T_H1: T helper 1 cells; T_H2: T helper 2 cells; T_H17:Thelper17cells; T_{REG}: regulatory T cells; MAIT: mucosal-associated invariant T cells; cT_{FH}: circulating follicular helper T cells; T_{FR}: T follicular regulatory cells.



Supplemental Figure 4. Inflammation-related proteins displaying significant changes between RPF patients (n=8) at and age- and sex- matched healthy controls (n=8). Shown are their protein quantification levels (NPX) in four assessments: 0: baseline, before treatment; 12: 12 weeks of the treatment; 48: 48 weeks of the treatment; ctrl: age- and sex- matched healthy controls. Statistical tests were employed as follows: 0-ctrl, t-test; 48-ctrl: equivalence test; 0-12,12-48,0-48: paired t-test. *: adjusted P < 0.05; **: adjusted P < 0.005; ***: adjusted P < 0.0005.



Supplemental Figure 5. Inflammation-related proteins with likely normal plasma levels at the baseline but distinct levels after 48 weeks of treatment with the combined therapy. 8 patients with RPF and 8 age- and sex- matched controls were assessed. (A-F): AXIN1, CCL20, CXCL5, CXCL1, FGF-21 and SIRT2. NPX: protein quantification levels in the Olink platform. 0: baseline, before treatment; 12: 12 weeks of treatment; 48: 48 weeks of treatment; ctrl: age- and sex- matched healthy controls. Statistical tests were employed as follows: 0-ctrl, t-test; 48-ctrl: equivalence test; 0-12,12-48,0-48: paired t-test. *: adjusted P < 0.05; **: adjusted P < 0.005; ***: adjusted P < 0.0005.

Supplemental Tables

Supplemental Table 1. Recruitment criteria of patients in the RPF combined therapy trial.

Inclusion criteria (all of them):

1) 18-75 years old;
2) Diagnosed as idiopathic RPF by CT or MRI - for patients suspected to have secondary RPF or atypical idiopathic RPF, puncture biopsy was conducted for clarification;
3) Increased ESR and CRP levels caused by RPF or active lesions detected by imaging.

Exclusion criteria (either one of them):

1) Secondary retroperitoneal fibrosis;
2) Usage of any glucocorticoid (equivalent to >10 mg per day of prednisone), immunosuppressant, or biologic medication within 3 months prior to the enrollment;
3) Having any contraindication of glucocorticoid or sirolimus, allergic to sirolimus, or experienced serious adverse reactions from previous use of any of the above drugs;
4) Massive proteinuria (24-hour urine protein quantitation ≥3 g), moderate-to-severe anemia (hemoglobin <90 g/L), agranulocytosis (white blood cell count $<1.5\times10^9$/L or neutrophil count $<0.5\times10^9$/L), platelet count < 50,000, or interstitial pneumonia;
5) Uncontrollable diabetes, hypertension, hyperlipidemia, infection, or heart failure;
6) Any malignant tumor;
7) Other serious complications or general conditions that do not permit study enrollment;
8) Pregnancy or plan for pregnancy in the near future;
9) Unable to adhere to follow-up or refuses to provide consent.

Supplemental Table 2. Pairing scores for evaluating matching between disease pathology and drug pharmacology.

Overlap of Enrichment Terms						
Category	Pharmacology_sirolumus	Pathology	Pharmacology_prednisone	Pathology	Pharmacology_tamoxifen	Pathology
Input	50	50	50	50	50	50
Tier-1 overlap	10	10	7	7	4	4
Tier-2 overlap	4	4	5	4	3	6
Paring Scores						
Category	Sirolimus vs RPF		Prednisone vs RPF		Tamoxifen vs RPF	
Tire-1	0.50		0.35		0.20	
Tier-2 pharmacology	0.10		0.13		0.08	
Tier-2 pathology	0.10		0.10		0.15	
Total	0.70		0.58		0.43	

Supplemental Table 3. Olink quantified plasma inflammatory proteins in response to the combined therapy.

Abnormal level inflammatory proteins in RPF (n=25) ①			
Normal at 48W (n=6)	Group 1 ①+⑤+⑦	CCL23, OSM, TNF, TNFRSF9, TRAIL, VEGFA	
Abnormal at 48W (n=1)	Group 2 ①+④	IL6	
Uncertain at 48W(n=18)	Group 3 ①+⑥, ①+⑤+⑧	Group 3.1 Likely Normal (n=10)	CASP-8, CCL3, CD40, CXCL9, GDNF, IL18, IL8, MCP-1, TNFSF14
		Group 3.2 Likely Abnormal (n=8)	CCL19, CSF-1, EN-RAGE, HGF, IL-10RB, MCP-2, MCP-3, MMP-1, TGF-alpha
Normal level inflammatory proteins in RPF (n=35) ②			
Normal at 48W (n=34)	Group 4 ②+⑤	4E-BP1, ADA, CCL11, CCL25, CCL28, CCL4, CD244, CD5, CD6, CD8A, CDCP1, CST5, CX3CL1, DNER, FGF-19, FGF-5, Flt3L, IFN-gamma, IL-15RA, IL-17A, IL-18R1, IL7, LAP TGF-beta, LIF-R, MMP-10, NT-3, OPG, PD-L1, SCF, SLAMF1, TNFB, TRANCE, TWEAK, uPA	
Abnormal at 48W (n=0)	Group 5 ②+④	-	
Uncertain at 48W (n=1)	Group 6 ②+⑥	IL-17C	
Uncertain in RPF (n=15) ③			
Normal at 48W (n=9)	Group 7 ③+⑤	CXCL10, CXCL11, CXCL6, FGF-23, IL-12B, IL10, MCP-4, ST1A1, STAMBP	
Abnormal at 48W (n=0)	Group 8 ③+④	-	
Uncertain at 48W (n=6)	Group 9 ③+⑥	AXIN1, CCL20, CXCL1, CXCL5, FGF-21, SIRT2	

Classification was based on stringent criteria:

① Case : Control - Abnormal: t.test, Padjust <= 0.05
② Case : Control - Normal: t.test, Padjust > 0.05 & equivalence test, Padjust <= 0.05
③ Case : Control - Uncertain: t.test, Padjust > 0.05 & equivalence test, Padjust > 0.05
④ 48W : Control - Abnormal: t.test, Padjust <= 0.05
⑤ 48W : Control - Normal: t.test, Padjust > 0.05 & equivalence test, Padjust <= 0.05
⑥ 48W : Control - Uncertain: t.test, Padjust > 0.05 & equivalence test, Padjust > 0.05
⑦ Treatment-responsive: paired t.test, Padjust <= 0.1
⑧ Treatment-responsive: paired t.test, Padjust > 0.1

Supplemental Table 4. Antibodies used in flow cytometric analysis.

Antibodies	Source	Identifier
Alexa Fluor® 700 anti-human CD3 Antibody	Biolegend	Cat:317340; RRID: AB_2563408
FITC anti-human CD4 Antibody	Biolegend	Cat:357406; RRID: AB_2562357
PerCP anti-human CD8 Antibody	Biolegend	Cat:344708; RRID: AB_1967149
PE anti-human CD25 Antibody	Biolegend	Cat:302606; RRID: AB_314276
Brilliant Violet 510™ anti-human CD45RA Antibody	Biolegend	Cat:304142; RRID: AB_2561947
Brilliant Violet 605™ anti-human CD127 (IL-7Rα) Antibody	Biolegend	Cat:351334; RRID: AB_2562022
Brilliant Violet 421™ anti-human CD197 (CCR7) Antibody	Biolegend	Cat:353208; RRID: AB_11203894
Brilliant Violet 711™ anti-human TCR Vα7.2 Antibody	Biolegend	Cat:351732; RRID: AB_2629680
PE/Dazzle™ 594 anti-human CD161 Antibody	Biolegend	Cat:339940; RRID: AB_2565868
Brilliant Violet 650™ anti-human CD196 (CCR6) Antibody	Biolegend	Cat:353426; RRID: AB_2563869
Alexa Fluor® 647 Rat Anti-Human CXCR5 (CD185)	BD Biosciences	Cat:558113; RRID: AB_2737606
CD279 (PD-1) Monoclonal Antibody (eBioJ105 (J105)), Biotin, eBioscience™	Thermo Fisher	Cat:13-2799-82; RRID: AB_837120
CD194 (CCR4) Monoclonal Antibody (D8SEE), APC, eBioscience™	Thermo Fisher	Cat:17-1949-42; RRID: AB_2573176
PE-Cy™7 Streptavidin (SA)	BD Biosciences	Cat:557598; RRID: AB_10049577
PE-CF594 Mouse Anti-Human CD183 (CXCR3)	BD Biosciences	Cat:562451; RRID: AB_11153118