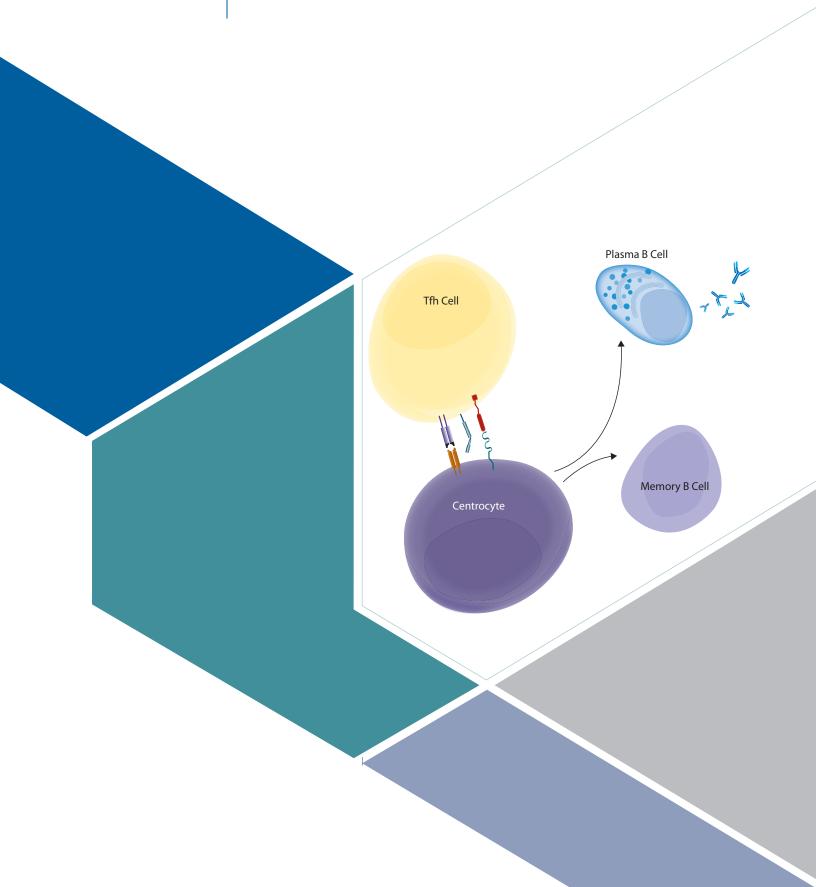


## Follicular Helper T Cells

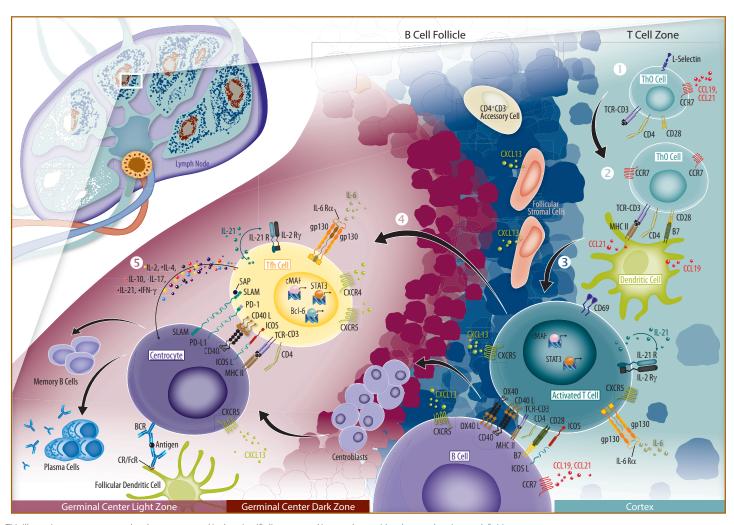


## Follicular Helper T Cells & Regulation of B Cell Immunity

Follicular helper T (Tfh) cells represent a functional subset of CD4+helper T (Th) cells that provides help for B cells to allow the formation of plasma cells and long-lived memory B cells. Tfh cells are characterized by the elevated expression of CXCR5, CD40L, OX40, ICOS, PD-1, Bcl-6, SLAM receptors, and IL-21. Though other Th subsets express these proteins, it is the relatively high expression levels that delineates Tfh cells and enhances their capacity to facilitate antibody production. Tfh cells are believed to be involved in angioimmunoblastic T cell lymphoma and several autoimmune diseases, including systemic lupus erythematosus and Sjogren's syndrome.

Though the complete differentiation process for Tfh cells is still being investigated, it has been shown that naïve CD4+T (Th0) cells expressing CCR7 chemokine receptor are chemoattracted to the T cell zone of the secondary lymphoid tissue by CCL19 and CCL21 (1). In the T cell zone, Th0 cells are activated by antigen-presenting dendritic cells and express CD40L, OX40, and ICOS (2). These activated T cells migrate to the edge

of the B cell follicle where they interact with antigen-primed B cells (3). The T cells also respond to IL-6 with the activation of the transcription factors cMAF and STAT3, and the induction of IL-21 expression. IL-6 and the autocrine action of IL-21 stimulate activated T cells to express Bcl-6, the master transcription factor that controls Tfh cell differentiation. Bcl-6, a transcriptional repressor, suppresses factors that mediate the differentiation of Th1, Th2, and Th17 cells. In addition, Bcl-6 indirectly induces the expression of accessory proteins, such as CXCR4 and PD-1, by repressing clusters of microRNAs that negatively regulate these molecules. The synergistic actions of Bcl-6 and cMAF, in conjunction with CD28, OX40, and ICOS stimulation in Tfh cells, induce a sustained increase in CXCR5 expression. CXCR5 directs migration into B cell follicles where Tfh cells interact with germinal center B cells called centrocytes (4). Tfh cells secrete IL-10, IL-21, and small amounts of IL-2, IL-4, IL-17, and IFN-γ, to stimulate centrocytes to generate antibodyproducing plasma cells and memory B cells (6).



 $This \it{ illustration represents general pathways suggested in the scientific \it{ literature and is not to be considered comprehensive nor definitive.} \\$ 

## **Abbreviation Key**

Bcl-6 B cell lymphoma-6
CD40 L CD40 Ligand
CR Complement Receptor
FcR Fc Receptor

ICOS Inducible T cell Co-stimulator

ICOS L ICOS Ligand OX40 L OX40 Ligand

PD-1 Programmed Death-1
PD-L1 Programmed Death Ligand-1
SAP SLAM-associated Protein

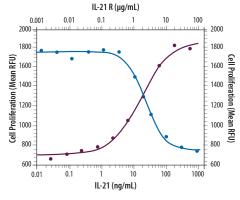
SLAM Signaling Lymphocytic Activation Molecule Receptor Family
STAT3 Signal Transducer and Activator of Transcription 3

## **Follicular Helper T Cell-Related Products**

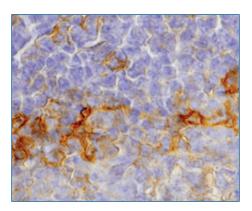
2B4/CD244/SLAMF4         H M         H M R         H M R           B7-H2/ICOS Ligand         H M         H M         H M           BcI-6         H M         H M         H M           BLAME/SLAMF8         H         H M         H M           BLIMP1         H M         H M         H M           BTLA/CD272         H M         H M         H M           CCL19/MIP-3β         H M R         H M R         H M           CCL21/6Ckine         H M R         H M         H M           CCR7         H M         M         H           CD4         H R CR F         H M R Ca CR F         H M           CD10/Neprilysin         H M         H M         H M           CD21         H M         H M         H M           CD20         H M         H M         H M           CD30/TNFRSF8         H M         H M         H M           CD30 Ligand/TNFSF8         H M R         H M         H M           CD40/TNFRSF5         H M R         H M         H M           CD40 Ligand/TNFSF5         H M R         H M         H M           CD40 Ligand/TNFSF5         H M R         H M         H M <t< th=""><th>Molecule</th><th>Recombinant &amp; Natural Proteins</th><th>Antibodies</th><th>ELISAs</th></t<>	Molecule	Recombinant & Natural Proteins	Antibodies	ELISAs
B7-H2/ICOS Ligand         H M         H M           BcI-6         H M         H M           BLAME/SLAMF8         H         H M         H M           BLIMP1         H M         H M         H M           BTLA/CD272         H M         H M R         H M R         H M           CCL19/MIP-3β         H M R         H M R         H M         H M           CCL21/6Ckine         H M R         H M         H M         H M           CD2F-10/SLAM9         H M         M         M	2B4/CD244/SLAMF4	НМ	н м	
BcI-6         H M         H M           BLAME/SLAMF8         H         H M         H M           BLIMP1         H M         H M         H M           BTLA/CD272         H M         H M R         H M R         H M           CCL19/MIP-3β         H M R         H M R         H M         H M           CCL21/6Ckine         H M R         H M         H M         H M           CD2F-10/SLAM9         H M         M         M         M           CD4         H R CR F         H M R Ca CR F         CD10/Neprilysin         H M         H M         H M         H M         M         M         M         M         CD21         H M         H M         H M         H M         H M         H M         H M         H M         H M         H M         M	Akt		HMR	HMR
BLAME/SLAMF8         H         H M         H M           BLIMP1         H M         H M         H M           BTLA/CD272         H M         H M R         H M R         H M           CCL19/MIP-3β         H M R         H M R         H M         H M           CCL21/6Ckine         H M R         H M         H M         H M           CD2F-10/SLAM9         H M         M         M         C           CD4         H R CR F         H M R Ca CR F         C           CD10/Neprilysin         H M         H M         H M           CD21         H         H         H         H           CD28         H M         H M         H M         H M           CD30/TNFRSF8         H M         H M         H M         H M           CD30 Ligand/TNFSF8         H M R         H M         H M         H M           CD40/TNFRSF5         H M R         H M         H M         H M           CD40/TNFRSF5         H M R         H M         H M         H M           CD48/SLAMF2         H M R         H M         H M         H M           CD48/SLAMF5         H M         H M         H M         H	B7-H2/ICOS Ligand	НМ	н м	
BLIMP1         H M         H M         H M           CCL19/MIP-3β         H M R         H M R         H M R         H M           CCL21/6Ckine         H M R         H M         H M         H M           CCR7         H M         M         M         CD2F-10/SLAM9         H M         M         M         M         M         CD2F-10/SLAM9         H M         M         M         M         M         M         M         CD2F-10/SLAM9         H M         M         M         M         M         M         M         M         CD4         H M         M	Bcl-6		н м	
BTLA/CD272         H M         H M R         H M R         H M M           CCL19/MIP-3β         H M R         H M R         H M M           CCL21/6Ckine         H M R         H M         H M           CCR7         H M         M         Image: Model of the color of th	BLAME/SLAMF8	Н	н м	
CCL19/MIP-3β         H M R         H M R         H M M           CCL21/6Ckine         H M R         H M         H M           CCR7         H M         M         M           CD2F-10/SLAM9         H M         M         M           CD4         H R CR F         H M R Ca CR F         CD10/Neprilysin         H M         H M         H M           CD21         H         H M         H M         H M         M         M         M         CD228         H M         H M         H M         M	BLIMP1		н м	
CCL21/6Ckine         H M R         H M         H M           CCR7         H M         M         M           CD2F-10/SLAM9         H M         M         M           CD4         H R CR F         H M R Ca CR F         M           CD10/Neprilysin         H M         H M         H M           CD21         H         H         H           CD28         H M         H M         H M           CD30/TNFRSF8         H M         H M         H M           CD30 Ligand/TNFSF8         H M         H M         M           CD35         H         H         H         M           CD40/TNFRSF5         H M R         H M         H M         H M           CD40 Ligand/TNFSF5         H M R         H M         H M         M           CD48/SLAMF2         H M         H M         H M         M           CD69         H M         H M         H M         H           CD200         H M         H M R         H         H           CD200 R1         H M         H M         H M         H           CXCR4         H M         H M         H         H           CXCR5 <td< td=""><td>BTLA/CD272</td><td>НМ</td><td>н м</td><td></td></td<>	BTLA/CD272	НМ	н м	
CCR7         H M           CD2F-10/SLAM9         H M         M           CD4         H R CR F         H M R Ca CR F           CD10/Neprilysin         H M         H M         H M           CD21         H         H         H           CD28         H M         H M         H M           CD30/TNFRSF8         H M         H M         H M           CD30 Ligand/TNFSF8         H M         H M         M           CD35         H         H         H         H           CD40/TNFRSF5         H M R         H M         H M         H M           CD40/INFRSF5         H M R         H M         H M         M           CD48/SLAMF2         H M         H M         M         M           CD69         H M         H M         H M         H           CD200         H M         H M R         H         H           CD200         H M         H M         H M         H           CD229/SLAMF3         H M         H M         H M         H           CXCR4         H M         H M F         H M         H M           CXCR5         H M R F         H M R F         H M	CCL19/MIP-3β	HMR	HMR	НМ
CD2F-10/SLAM9         H M         M           CD4         H R CR F         H M R Ca CR F           CD10/Neprilysin         H M         H M         H M           CD21         H         H         H           CD28         H M         H M         H M           CD30/TNFRSF8         H M         H M         H M           CD30 Ligand/TNFSF8         H M         H M         M           CD35         H         H         H         H M           CD40/TNFRSF5         H M R         H M         H M         H M           CD40 Ligand/TNFSF5         H M R         H M         H M         M           CD48/SLAMF2         H M         H M         M         M           CD69         H M         H M         H M         H M         H M           CD200         H M         H M R         H M         H M         H M           CD229/SLAMF3         H M<	CCL21/6Ckine	HMR	н м	н м
CD4         H R CR F         H M R Ca CR F           CD10/Neprilysin         H M         H M         H M           CD21         H         H         H           CD28         H M         H M         H M           CD30/TNFRSF8         H M         H M         H M           CD30 Ligand/TNFSF8         H M         H M         M           CD35         H         H         H         H           CD40/TNFRSF5         H M R         H M         H M         H M           CD40 Ligand/TNFSF5         H M R         H M         H M         H M           CD48/SLAMF2         H M         H M         M         M           CD69         H M         H M         H M         M           CD200         H M         H M R         H M         H           CD200         H M         H M         H M         H           CD229/SLAMF3         H M         H M         H M         H M           CXCR13/BLC/BCA-1         H M         H M         H M         H M           CXCR5         H M R F         H M R F         H M         H M           Fas/TNFRSF6/CD95         H M R F         H M         H M	CCR7		н м	
CD10/Neprilysin         H M         H M         H M           CD21         H         H         H           CD28         H M         H M         H M           CD30/TNFRSF8         H M         H M         H M           CD30 Ligand/TNFSF8         H M         H M         M           CD35         H         H         H         H           CD40/TNFRSF5         H M R         H M         H M         H M           CD40 Ligand/TNFSF5         H M R         H M         H M         H M           CD48/SLAMF2         H M         H M         M         M           CD69         H M         H M         H M         M           CD84/SLAMF5         H M         H M R         H         H           CD200         H M         H M         H M R         H         H           CD203         H M         H M         H M         H         H         H         M         H         M         H         M         H         M         H         M         H         M         H         M         H         M         H         M         H         M         M         M         H <t< td=""><td>CD2F-10/SLAM9</td><td>НМ</td><td>М</td><td></td></t<>	CD2F-10/SLAM9	НМ	М	
CD21         H         H         H         M	CD4	H R CR F	H M R Ca CR F	
CD28         H M         H M         H M         H M         H M         H M         H M         H M         H M         H M         H M         M         CD30 Ligand/TNFSF8         H M         H M         H M         M         M         CD35         H M         H M         H M         H M         H M         H M         H M         H M         H M         H M         H M         H M         H M         H M         H M         H M         H M         M         CD48/SLAMF2         H M	CD10/Neprilysin	НМ	н м	НМ
CD30/TNFRSF8         H M         H M         H M         H M           CD30 Ligand/TNFSF8         H M         H M         M           CD40/TNFRSF5         H M R         H M         H M           CD40 Ligand/TNFSF5         H M R         H M         H M           CD48/SLAMF2         H M         H M         M           CD69         H M         H M         H           CD200         H M         H M R         H           CD200         H M         H M         H M           CD203 R1         H M         H M         H M           CCACC/SLAMF3         H M         H M         H M           CXCC13/BLC/BCA-1         H M         H M         H M           CXCR4         H M F         H M R F         H M           Fas/TNFRSF6/CD95         H M R F         H M R F         H M	CD21	Н	Н	
CD30 Ligand/TNFSF8         H M         H M         M           CD35         H         H         H           CD40/TNFRSF5         H M R         H M         H M           CD40 Ligand/TNFSF5         H M R         H M         H M           CD48/SLAMF2         H M         H M         M           CD69         H M         H M         H M           CD84/SLAMF5         H M         H M R         H           CD200         H M         H M R         H           CD200 R1         H M         H M         H M           CRACC/SLAMF3         H M         H M         H M           CXCC13/BLC/BCA-1         H M         H M         H M           CXCR4         H M F         H M R F         H M           Fas/TNFRSF6/CD95         H M R F         H M R F         H M	CD28	НМ	н м	
CD35         H         H         H         M	CD30/TNFRSF8	нм	н м	НМ
CD40/TNFRSF5         H M R         H M         H M           CD40 Ligand/TNFSF5         H M R         H M         H M           CD48/SLAMF2         H M         H M         M           CD69         H M         H M         H           CD84/SLAMF5         H M         H         H           CD200         H M         H M R         H           CD200 R1         H M         H M         H M           CD229/SLAMF3         H M         H M         H M           CRACC/SLAMF7         M         H M         H M           CXCL13/BLC/BCA-1         H M         H M         H M           CXCR4         H M F         H M R F         H M           Fas/TNFRSF6/CD95         H M R F         H M R F         H M	CD30 Ligand/TNFSF8	нм	н м	М
CD40 Ligand/TNFSF5         H M R         H M         H M           CD48/SLAMF2         H M         H M         M           CD69         H M         H M         M           CD84/SLAMF5         H M         H         M           CD200         H M         H M R         H           CD200 R1         H M         H M         M           CD229/SLAMF3         H M         H M         M           CRACC/SLAMF7         M         H M         H M           CXCL13/BLC/BCA-1         H M         H M F         H M F           CXCR4         H M F         H M R F         H M R F         H M           Fas/TNFRSF6/CD95         H M R F         H M R F         H M           Fcy RII/CD32         H M         H M         H M	CD35	Н	Н	
CD48/SLAMF2         H M         H M         M           CD69         H M         H M         M           CD84/SLAMF5         H M         H         M           CD200         H M         H M R         H           CD200 R1         H M         H M         M           CD229/SLAMF3         H M         H M         M           CRACC/SLAMF7         M         H M         H M           CXCL13/BLC/BCA-1         H M         H M         H M           CXCR4         H M F         H M F         H M R F         H M           Fas/TNFRSF6/CD95         H M R F         H M R F         H M           Fcy RII/CD32         H M         H M         H M	CD40/TNFRSF5	H M R	н м	НМ
CD69         H M         H M           CD84/SLAMF5         H M         H           CD200         H M         H M R         H           CD200 R1         H M         H M         CD29/SLAMF3         H M           CRACC/SLAMF7         M         H M         CD29/SLAMF3         H M           CXCL13/BLC/BCA-1         H M         H M         H M           CXCR4         H M F         CXCR5         H M           Fas/TNFRSF6/CD95         H M R F         H M R F         H M           Fcy RII/CD32         H M         H M         CXCR5	CD40 Ligand/TNFSF5	H M R	н м	НМ
CD84/SLAMF5         H M         H         H         H         CD200         H M         H M R         H         H         M         CD200 R1         H M         H M         H M         H M         CD229/SLAMF3         H M         H M         H M         CRACC/SLAMF7         M         H M         H M         H M         CXCL13/BLC/BCA-1         H M         H M         H M         H M         CXCR4         H M F         CXCR4         H M F         H M R F         H M R F         H M         H M         Fcy RII/CD32         H M         H M         H M         Fcy RII/CD32         H M         H M         Fcy RII/CD32         Fcy RII/CD32         H M         Fcy RII/CD32         Fc	CD48/SLAMF2	нм	н м	М
CD200         H M         H M R         H           CD200 R1         H M         H M         H M           CD229/SLAMF3         H M         H M         C           CRACC/SLAMF7         M         H M         H M           CXCL13/BLC/BCA-1         H M         H M         H M           CXCR4         H M F         C         C           Fas/TNFRSF6/CD95         H M R F         H M R F         H M           Fcy RII/CD32         H M         H M         C	CD69	нм	н м	
CD200 R1	CD84/SLAMF5	нм	Н	
CD229/SLAMF3         H M         H M           CRACC/SLAMF7         M         H M           CXCL13/BLC/BCA-1         H M         H M         H M           CXCR4         H M F         CXCR5         H M           Fas/TNFRSF6/CD95         H M R F         H M R F         H M           Fcy RII/CD32         H M         H M         H M	CD200	НМ	H M R	Н
CRACC/SLAMF7         M         H M           CXCL13/BLC/BCA-1         H M         H M         H M           CXCR4         H M F         CXCR5         H M         H M R F         H M R F         H M           Fas/TNFRSF6/CD95         H M R F         H M<	CD200 R1	нм	н м	
CXCL13/BLC/BCA-1         H M         H M         H M           CXCR4         H M F           CXCR5         H M         H M R F         H M R F           Fas/TNFRSF6/CD95         H M R F         H M R F         H M           Fcy RII/CD32         H M         H M         H M	CD229/SLAMF3	НМ	н м	
CXCR4         H M F           CXCR5         H M           Fas/TNFRSF6/CD95         H M R F         H M R F         H M           Fcy RII/CD32         H M         H M         H M	CRACC/SLAMF7	M	н м	
CXCR5	CXCL13/BLC/BCA-1	НМ	н м	НМ
Fas/TNFRSF6/CD95         H M R F         H M R F         H M         H M           Fcy RII/CD32         H M         H         M	CXCR4		HMF	
Fcy RII/CD32 H M	CXCR5		НМ	
	Fas/TNFRSF6/CD95	HMRF	HMRF	НМ
GATA-3 H M	Fcγ RII/CD32		н м	
	GATA-3		НМ	
ICOS H M H M	ICOS	НМ	н м	
IFN-γ H M R P B Ca CR E F H M R P B Ca CR E F RM V H M R P B Ca CR E F Pr	IFN-γ			H M R P B Ca CR E F Pr

Molecule	Recombinant & Natural Proteins	Antibodies	ELISAs
IL-4	H M R P B Ca CR E F Rb RM	H M R P B Ca CR E F Rb	H M R P Ca CR E F Rb
IL-4 Rα	НМ	НМ	
IL-5	H M R P B Ca E F RM	HMRPCaEF	HMF
IL-6	H M R P Ca CR E F	H M R P Ca CR E F Pr	H M R P B Ca CR F Rb
IL-6 Rα	нм	НМ	нм
IL-10	H M R P Ca CR E F V	H M R P Ca CR E F V	H M R P Ca E F GP
IL-13	H M R Ca CR RM	H M R Ca	нм
IL-17/IL-17A	H M R Ca	H M Ca Pr	н м Са
IL-21	H M Ca Rb	M Ca	М
IL-21 R	HMR	НМ	
Jak1		HMR	
Jak2		MR	
NFATC1		Н	
NTB-A/SLAMF6/ Ly-108	нм	нм	
OX40/TNFRSF4	H M R	НМ	
OX40 Ligand/TNFSF4	HMR	НМ	М
PD-1	н м см	НМ	нм
PD-L1/B7-H1	НМ	НМ	H CM
PD-L2	H M CM	НМ	Н
PI 3-Kinase p55γ		HMR	
PI 3-Kinase p85 $\alpha$		HMR	
PI 3-Kinase p85 $\beta$		Н	
PI 3-Kinase p110β		Н	
PI 3-Kinase p110 $\delta$		Н	
PI 3-Kinase p110γ		Н	
PTEN	Н	HMR	
SHP-1	Н	HMR	
SHP-2	Н	H M R	HMR
SLAM/CD150	НМ	нм	нм
STAT3		H M R	НМ
Tyk2		Н	
Vav-1		нм	

H Human M Mouse R Rat B Bovine Ca Canine CM Cynomolgus Monkey CR Cotton Rat E Equine F Feline GP Guinea Pig P Porcine Pr Primate Rb Rabbit RM Rhesus Macaque V Viral



Inhibition of IL-21 Activity by Soluble IL-21 Receptor. Recombinant Mouse IL-21 (Catalog # 594-ML) stimulates the proliferation of N1186 HTLV-1-infected human T cells (red line), measured by resazurin fluorescence (Catalog # AR002). The stimulatory effect induced by 100 ng/mL IL-21 was inhibited in a dose-dependent manner by soluble Recombinant Mouse IL-21 R (Catalog # 596-MR; blue line).



ICOS in Human Tonsil. ICOS was detected in paraffin-embedded human tonsil tissue sections using the Human ICOS Antigen Affinity-purified Polyclonal Antibody (Catalog # AF169). The tissue was stained using the Anti-Goat HRP-DAB Cell and Tissue Staining Kit (Catalog # CTS008; brown) and counterstained with hematoxylin (blue).



















