

**Competition and synergism between individual tumor necrosis factor- α activities
determine granuloma structure during infection with *Mycobacterium tuberculosis***

Supplement 3: Supplementary Tables and Figures

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Table S1. Significant changes in granuloma variables at 200 days post-infection for deletion and depletion of combinations of two individual TNF activities versus the baseline control scenario¹. Sample granuloma structures for each deletion and depletion are shown in Figures 8 and S2. Apo: TNF-induced apoptosis; Rec: TNF-mediated recruitment; Act: TNF-mediated activation; Sec: TNF-induced chemokine/TNF secretion.

	Apo & Rec		Apo & Act		Apo & Sec		Act & Rec		Act & Sec		Rec & Sec	
	Del	Depl	Del	Depl	Del	Depl	Del	Depl	Del	Depl	Del	Depl
B _e	---	---	+++	+++	++	+++	+++	+++	+++	+++		
B _i	---	---	+++	+	--				+++	+++	+	+
Total T cells		+++	+++	+++	-	-	---	--			--	--
T _γ	+	+++	+++	+++		-	---	---			--	--
“Secretor” T _γ ²	-	-	--	+++	-							
T _c	+	+++	+++	+++	-		---	--			--	--
T _{reg}	+	+++	+++	+++								
Total Macrophages	+	+++	+++	+++			---	---			--	--
M _r		+++	+++	+++			---	---			--	---
M _i	---	---	+++		---	---			+++	+++	++	++
M _{ci}	---	---	+++	+					+			
M _a	++	+++	---	---	++	++	---	---	--	--		
TNF	+	+++	+++	+++			-		+++	+++		
Chemokines	+	+++	+++	+++					+++	+++		
Caseation	---	---	+++	---	+++	+++	+++	+++	+++	+++	++	+++
Granuloma Size	ND ³	ND ³	ND ³	ND ³			-		+++	++		

¹+ denotes a higher variable value for the deletion or depletion than the control scenario; - denotes a lower value. +++ (p < 0.0001); ++ (p < 0.001); + (p < 0.01). Significant negative correlations: --- (p < 0.0001); -- (p < 0.001); - (p < 0.01).

²Number of T_γ cells actively secreting IFN-γ.

³Granuloma structures lack distinct bounds for quantification in these cases.

Table S2. Significant changes in granuloma variables at 200 days post-infection for deletion and depletion of combinations of three individual TNF activities versus the baseline control scenario¹. Sample granuloma structures for each deletion and depletion are shown in Figures 8 and S2. Apo: TNF-induced apoptosis; Rec: TNF-mediated recruitment; Act: TNF-mediated activation; Sec: TNF-induced chemokine/TNF secretion.

	Rec, Act & Apo		Rec, Act & Sec		Rec, Apo & Sec		Act, Apo & Sec	
	Del	Depl	Del	Depl	Del	Depl	Del	Depl
B _e	+++	+++	+++	+++	++	+++	+	+++
B _i	+		+++	+++	--	-		+++
Total T cells	+++	+++	--	--	---	---		
T _γ	+++	+++	--	--	---	---		
“Secretor” T _γ ²	+++	+++			-	-		
T _c	+++	+++	--	-	---	---		
T _{reg}	+++	+++			--	-		
Total Macrophages	+++	+++	---	---	-	-		
M _r	+++	+++	---	---	-	-		
M _i			+++	+++	----	---		+++
M _{ci}	+						++	+++
M _a	---	---	--	--	+	++		
TNF	+++	+++	++	+++				+++
Chemokines	+++	+++	++	+++				+++
Caseation	---	---	+++	+++	++	+++		+++
Granuloma Size	ND ³	ND ³	+		-		+++	+++

¹+ denotes a higher variable value for the deletion or depletion than the control scenario; - denotes a lower value. +++ (p < 0.0001); ++ (p < 0.001); + (p < 0.01). Significant negative correlations: --- (p < 0.0001); -- (p < 0.001); - (p < 0.01).

²Number of T_γ cells actively secreting IFN-γ.

³Granuloma structures lack distinct bounds for quantification in these cases.

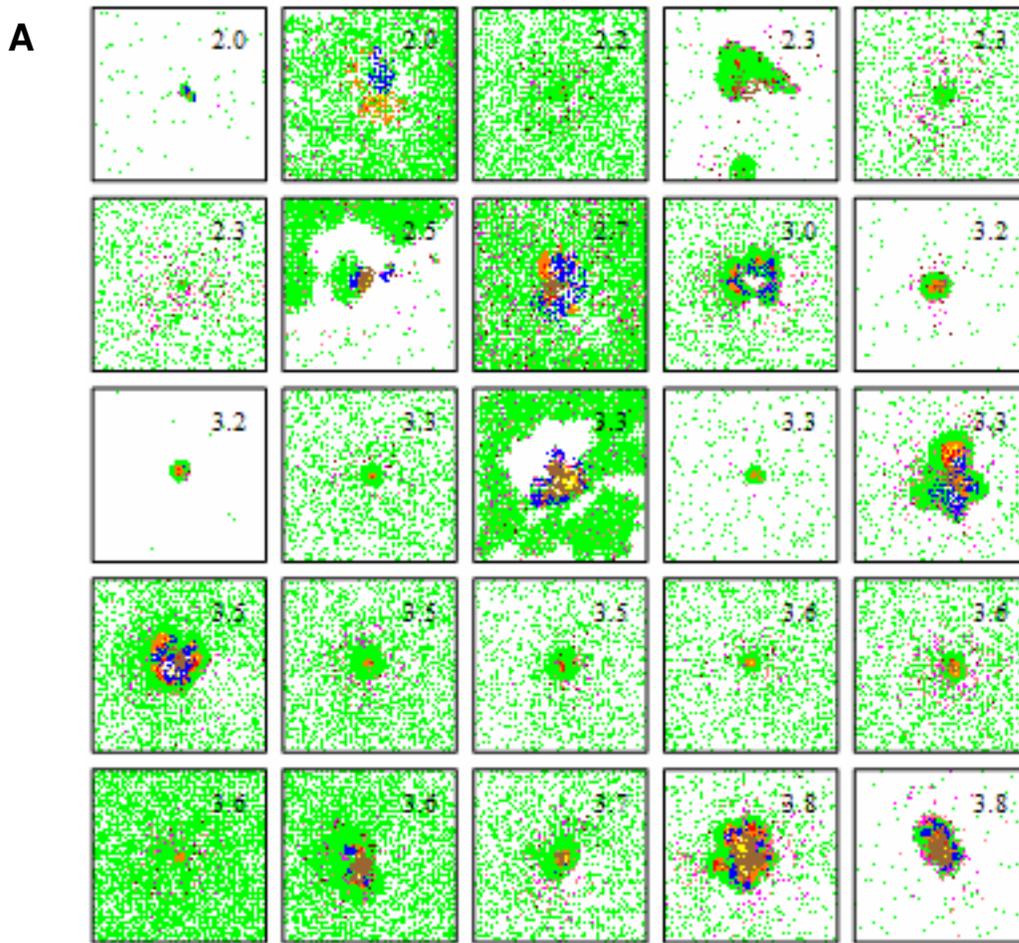


Figure S1. (This figure is 3 pages long.) Attainable granuloma structures 200 days post-infection from one run of global uncertainty analysis. Slides are sorted by number of extracellular bacteria from left to right and top to bottom. 80 total simulations that did not predict complete bacterial elimination are shown. Numbers indicate \log_{10} extracellular *M. tuberculosis* number. Cell types are colored as follows: green, orange, red and blue are resting, infected, chronically infected and activated macrophages, respectively; yellow, extracellular bacteria; brown, caseation; pink, purple and light blue, pro-inflammatory, cytotoxic, and regulatory T cells, respectively.

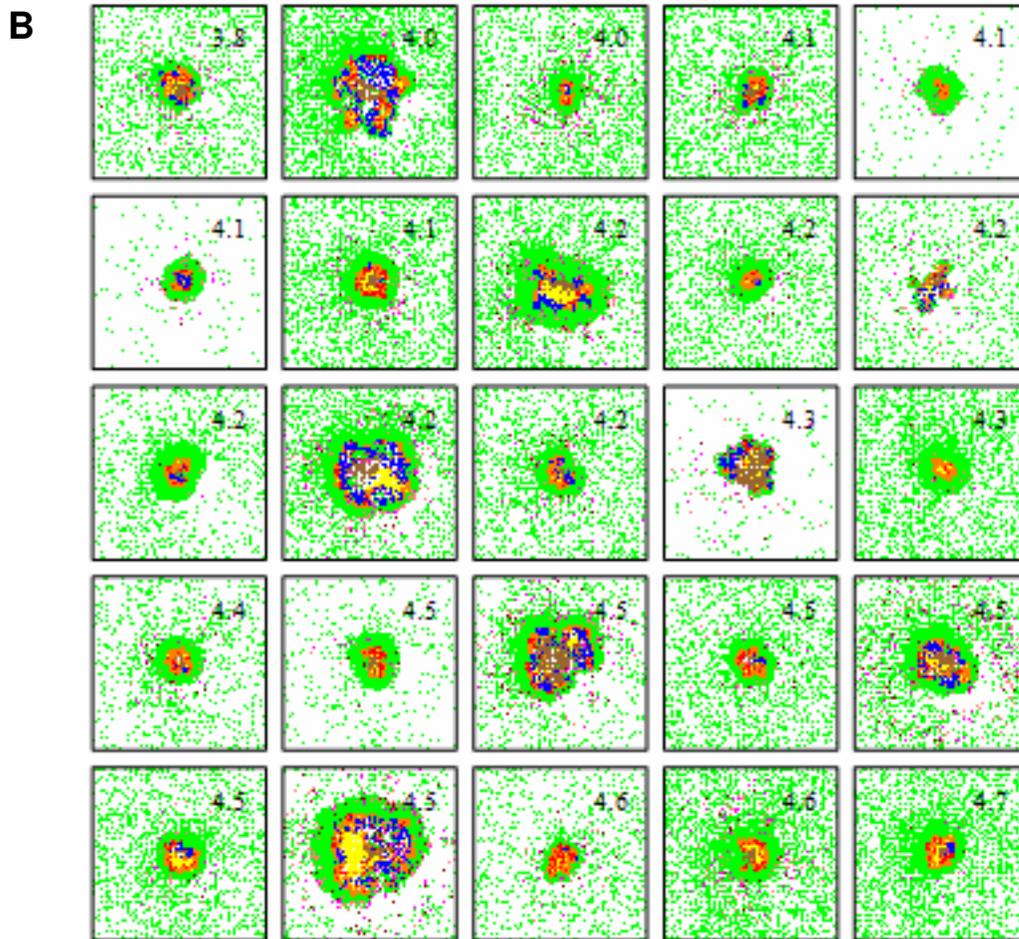


Figure S1B. (continued from previous page)

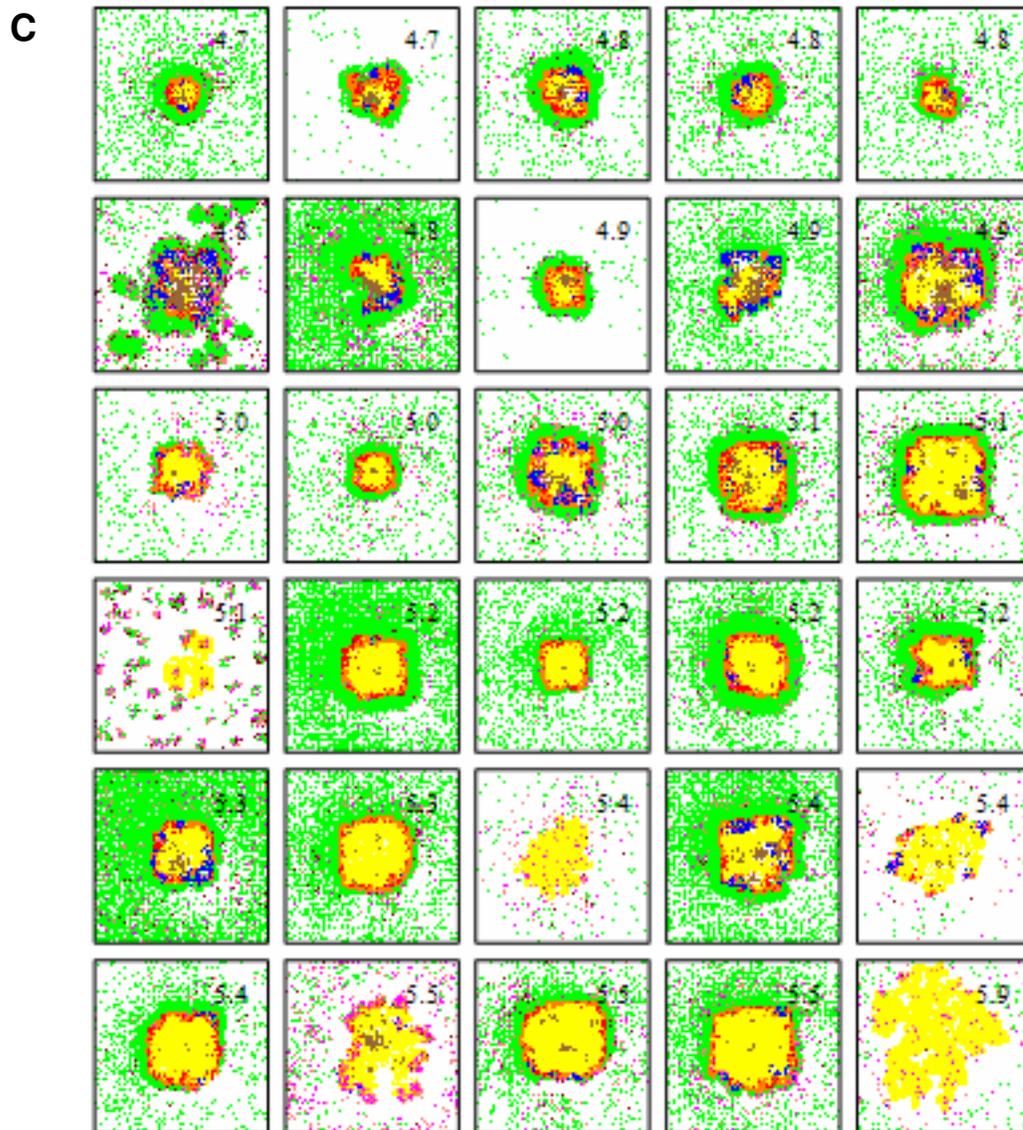


Figure S1C. (continued from previous page)

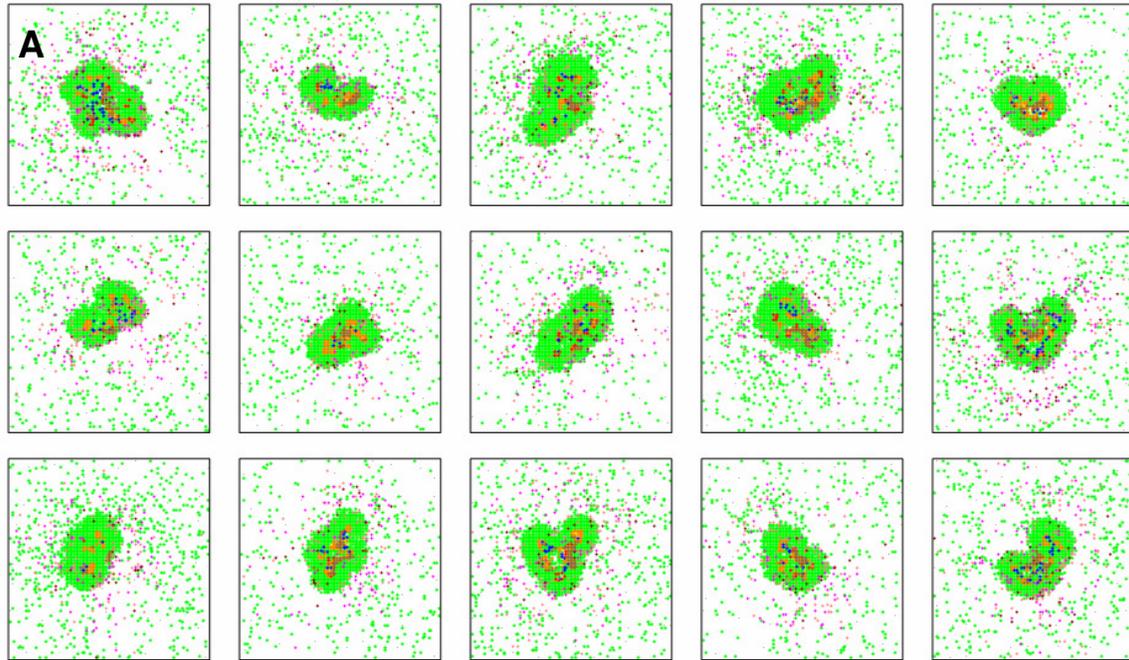


Figure S2. (This figure is 5 pages long.) Granuloma structures predicted for deletion and depletion of each specific TNF activity. Replicates of structures containing infection at day 200 are shown. A. Baseline case with all TNF activities present. B-I. Deletion and depletion, respectively, of: all TNF activity (B, C); TNF-induced recruitment activity (D, E); TNF effects on macrophage activation activity (F, G); and TNF-induced chemokine and TNF secretion from macrophages activities (H, I).

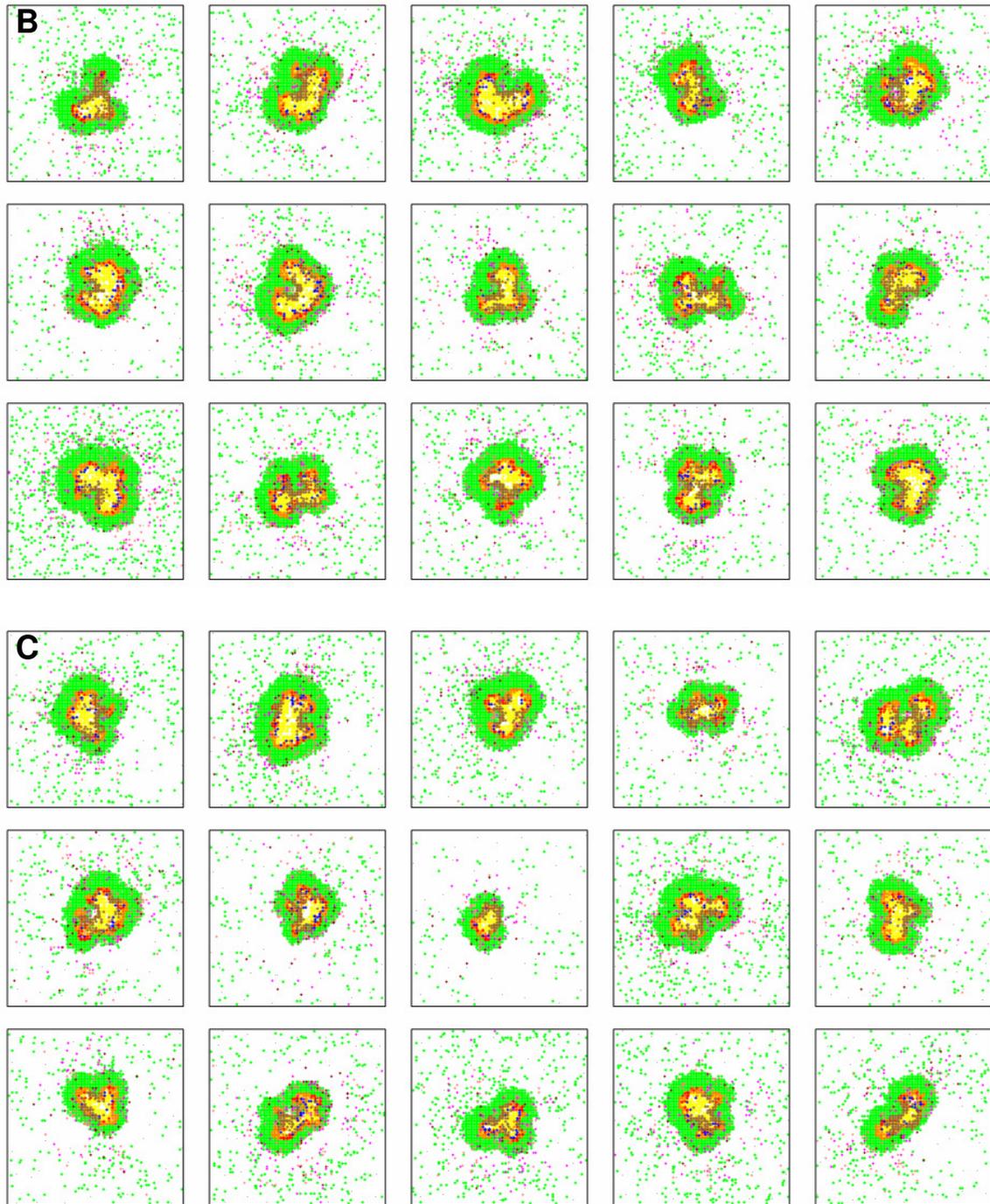


Figure S2 B-C. Deletion (B) and depletion (C) of all TNF activity.

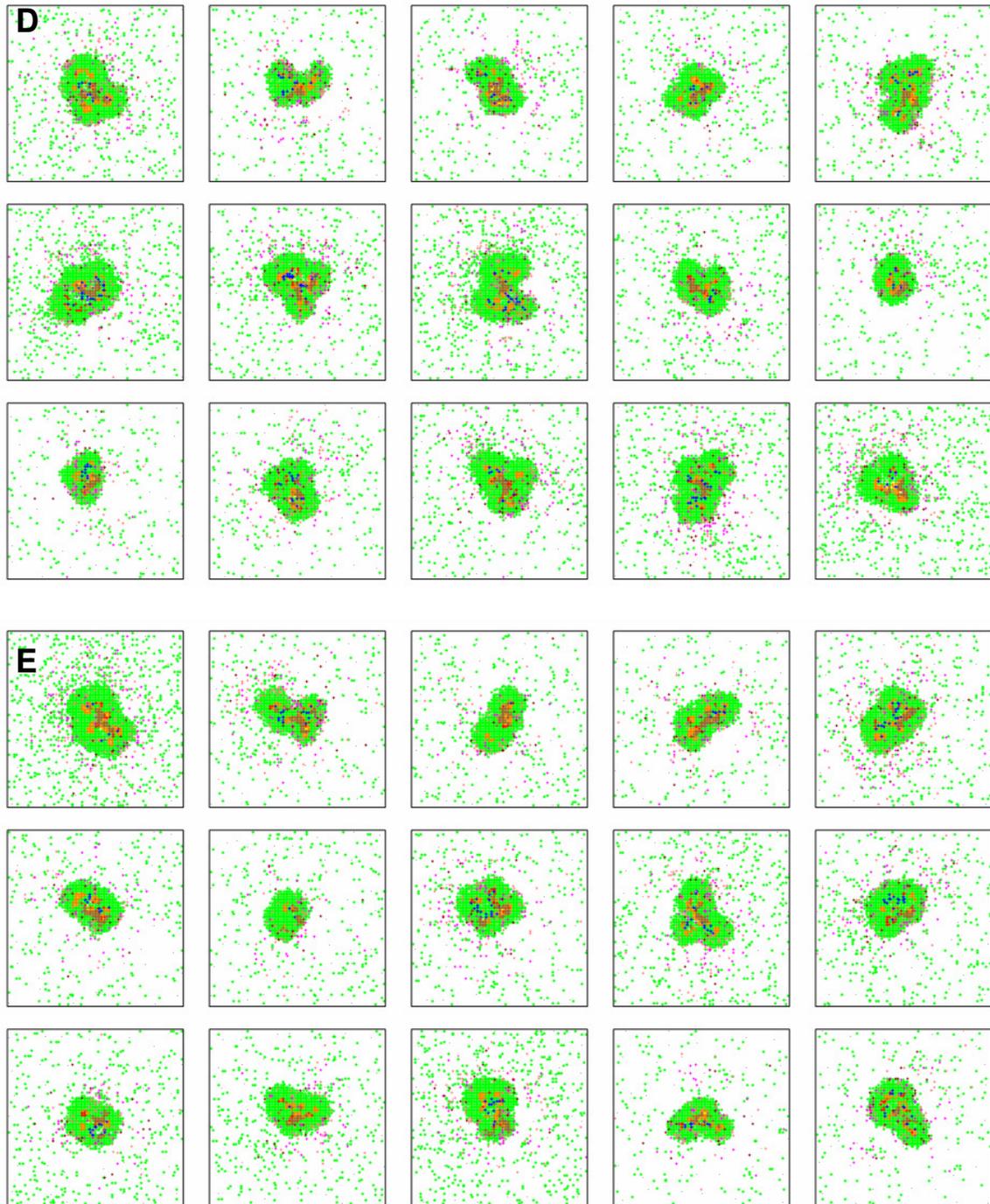


Figure S2 D-E. Deletion (D) and depletion (E) of TNF-induced recruitment.

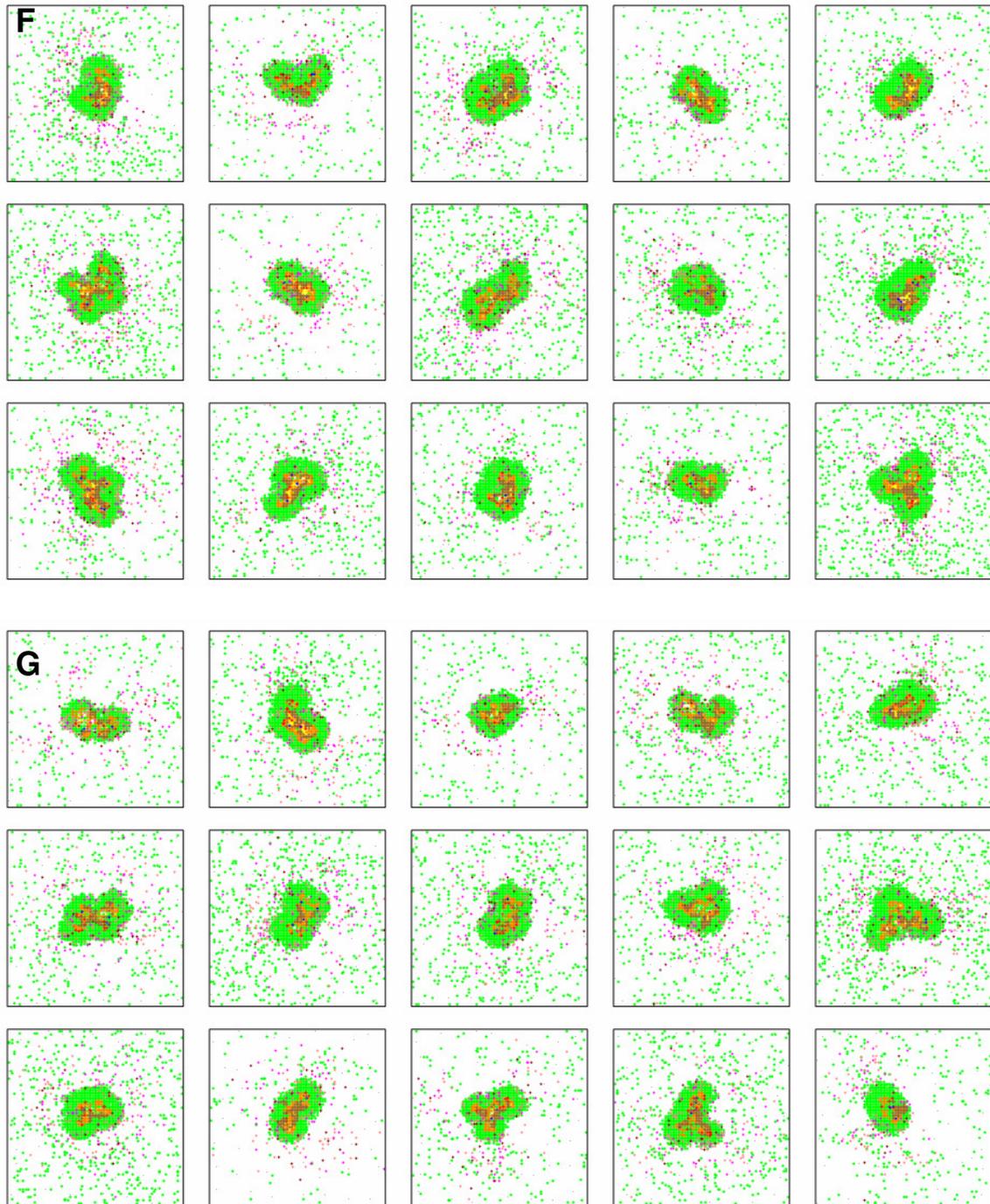


Figure S2 F-G. Deletion (F) and depletion (G) of TNF effects on macrophage activation.

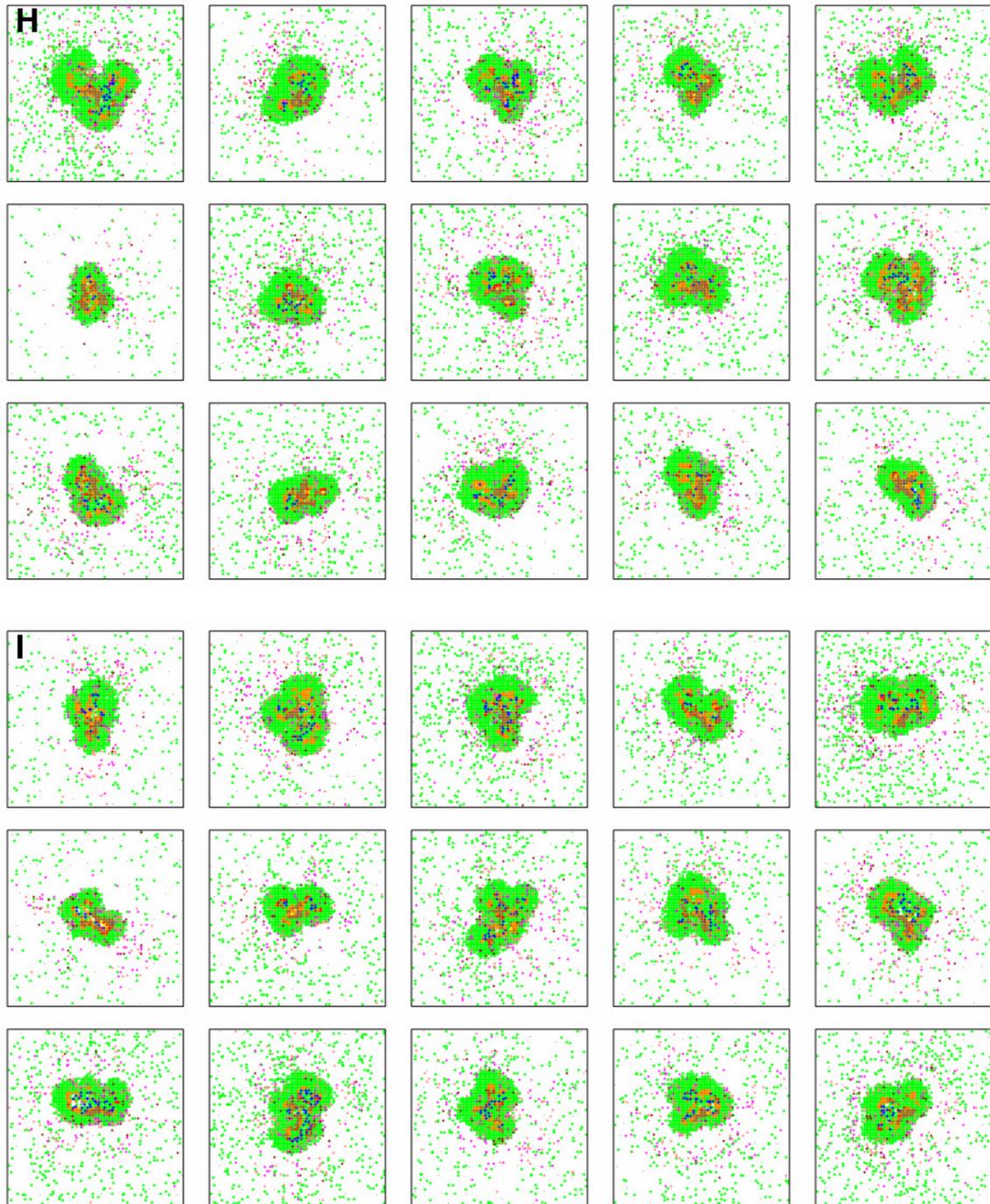


Figure S2 H-I. Deletion (H) and depletion (I) of TNF-induced chemokine and TNF secretion from macrophages.

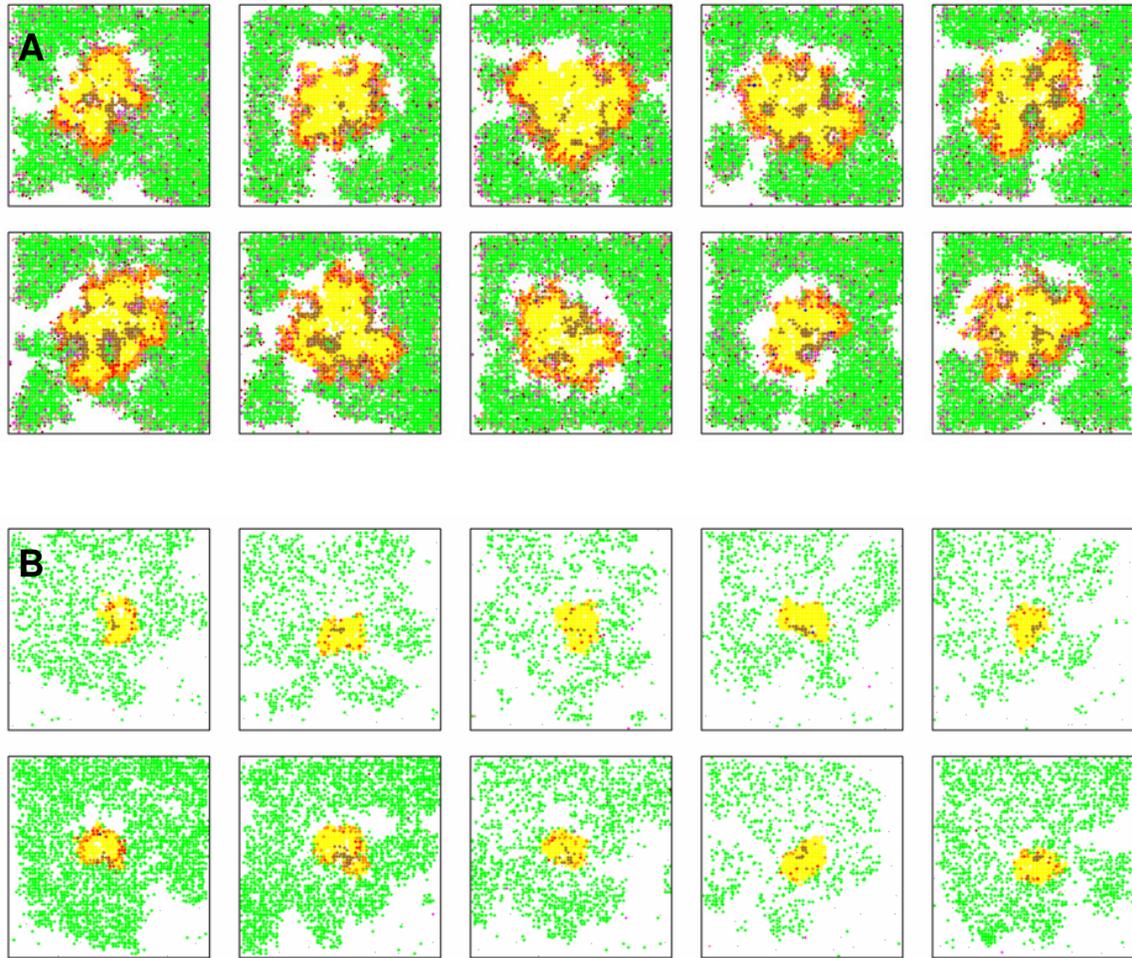


Figure S3. (This figure is 9 pages long.) Granuloma structures predicted for ten replicates of deletion and depletion of specific TNF activity combinations. Replicates of structures containing infection at day 200 are shown. A-R. Deletion and depletion, respectively, of: apoptosis & activation (A, B); apoptosis & secretion activities (C, D); activation & recruitment activities (E, F); activation & secretion activities (G, H); recruitment & secretion activities (I, J); recruitment, activation & secretion activities (K, L); recruitment, apoptosis & secretion activities (M, N); activation, apoptosis & secretion activities (O, P). Each activity refers to specific TNF-induced activities illustrated in Figure 1A. The combinations of apoptosis & recruitment deletion/depletion and recruitment, activation & apoptosis deletion/depletion are omitted due to complete bacterial elimination predicted for all simulations.

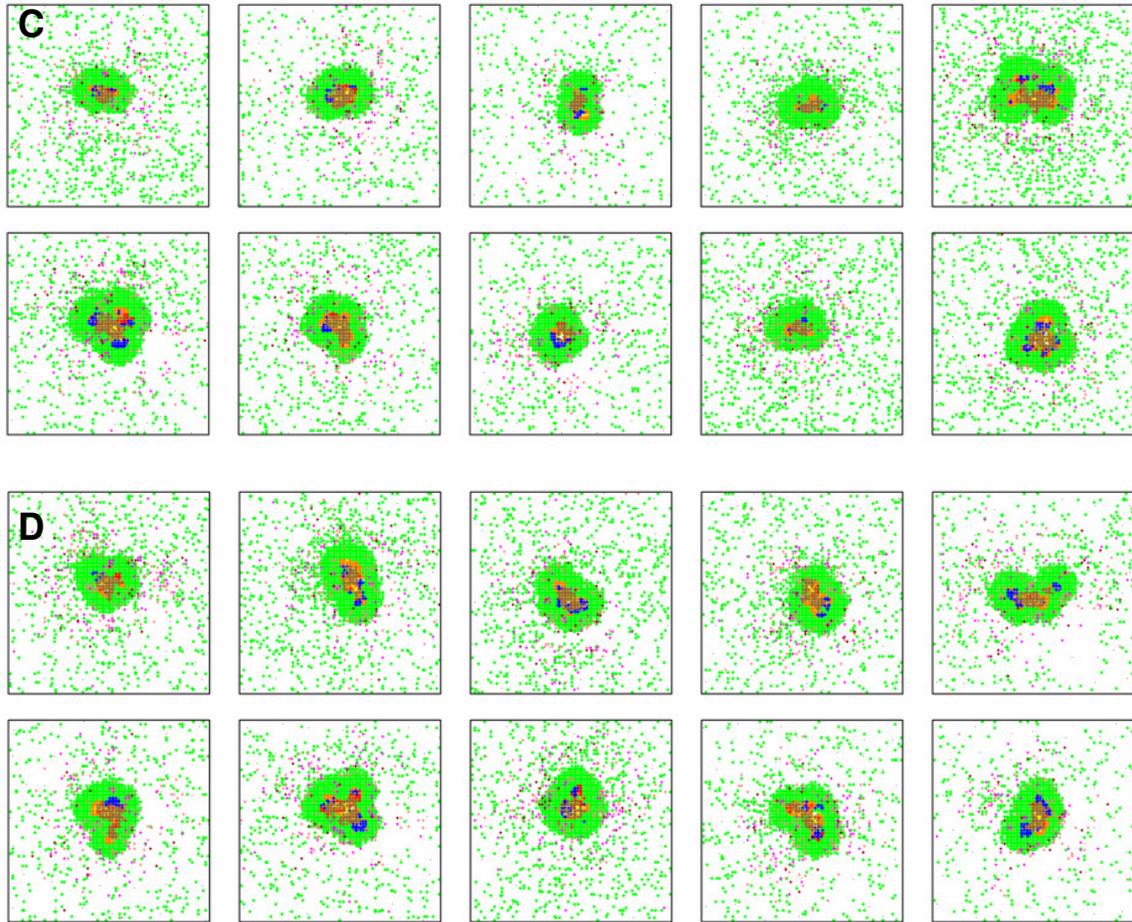


Figure S3 C-D. Deletion (C) and depletion (D) of TNF-induced apoptosis and chemokine/TNF secretion from macrophages.

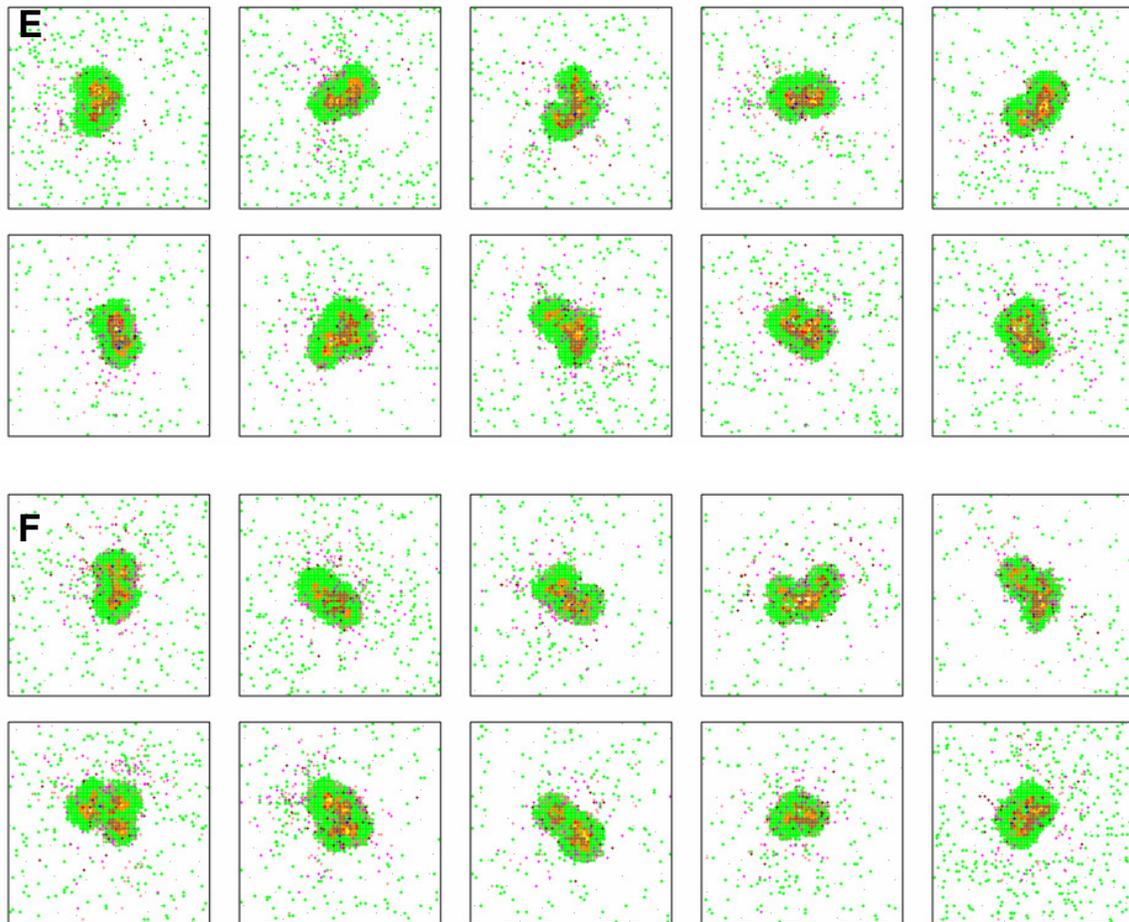


Figure S3 E-F. Deletion (E) and depletion (F) of TNF-induced macrophage activation activity and recruitment of immune cells.

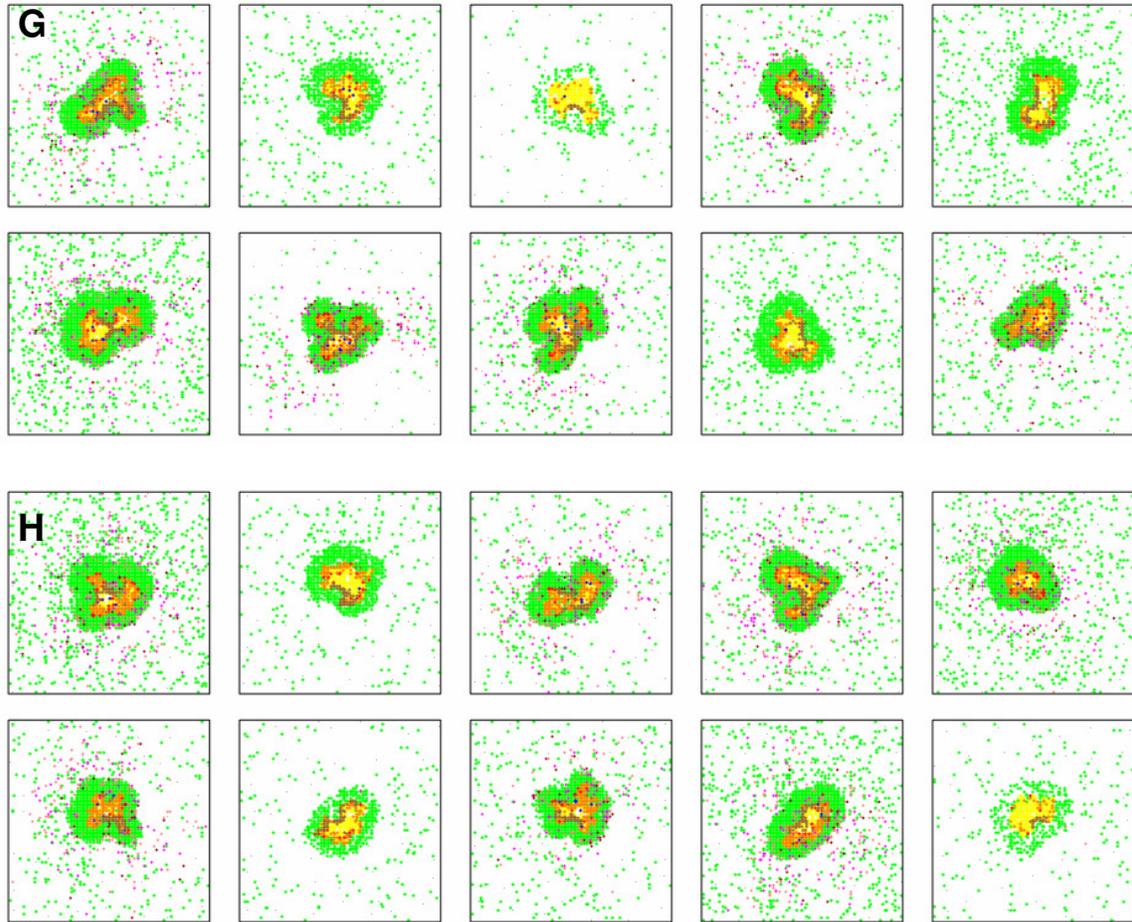


Figure S3 G-H. Deletion (G) and depletion (H) of TNF-induced macrophage activation and chemokine/TNF secretion from macrophages.

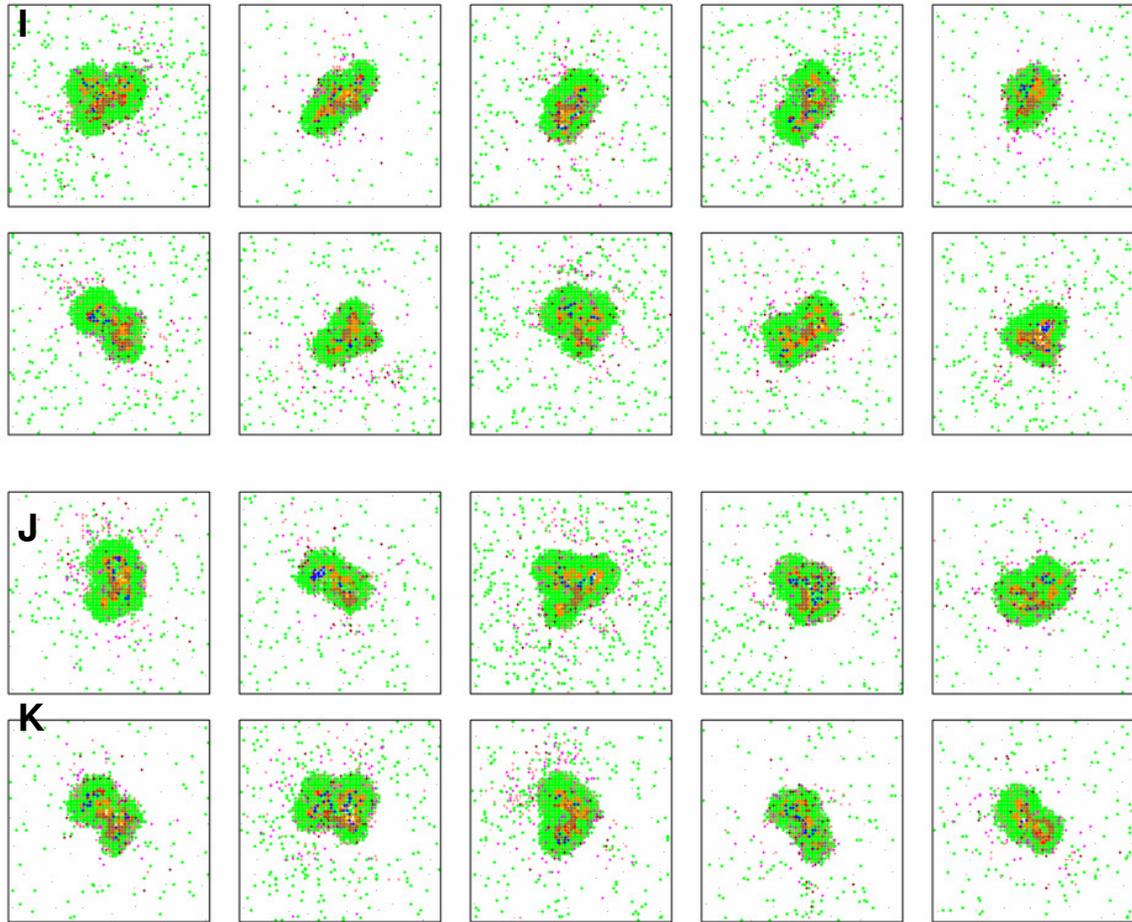


Figure S3 I-J. Deletion (I) and depletion (J) of TNF-induced immune cell recruitment and chemokine/TNF secretion from macrophages.

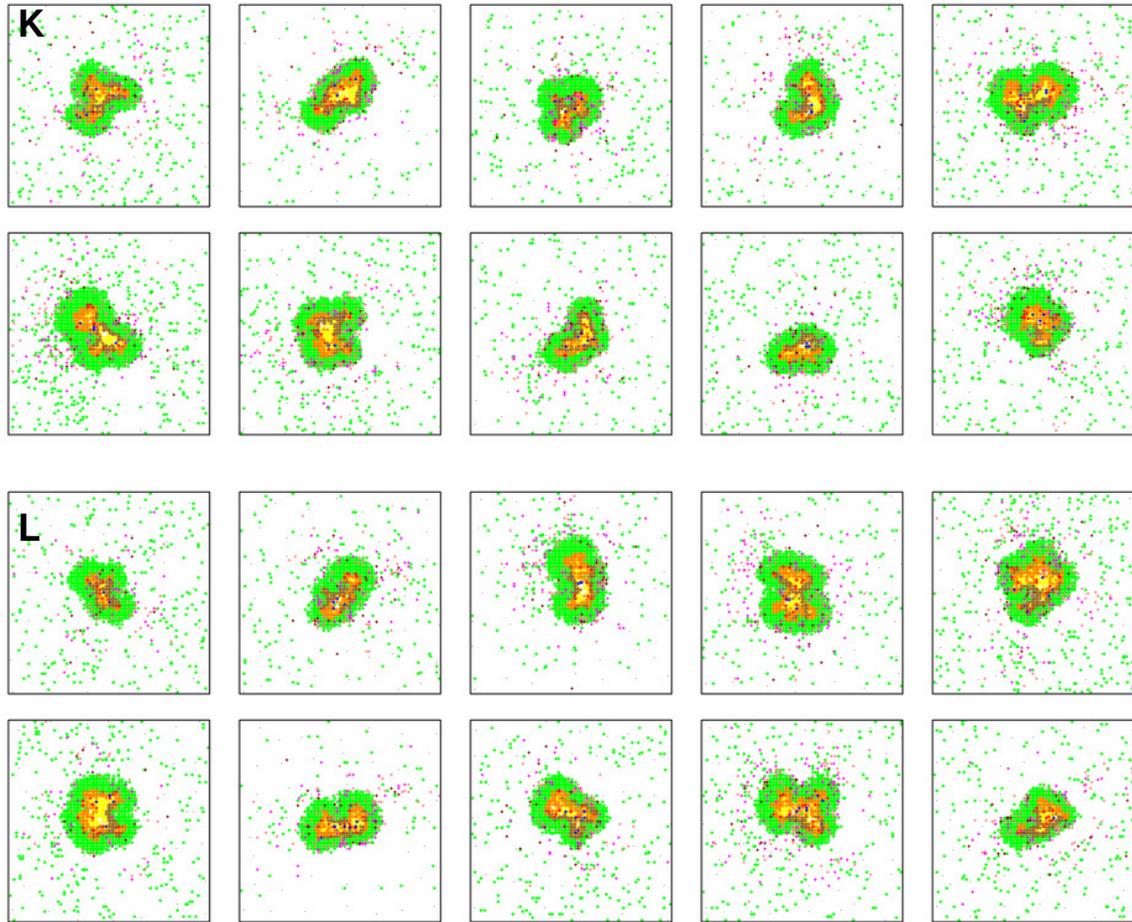


Figure S3 K-L. Deletion (K) and depletion (L) of TNF-induced immune cell recruitment, macrophage activation, and chemokine/TNF secretion from macrophages.

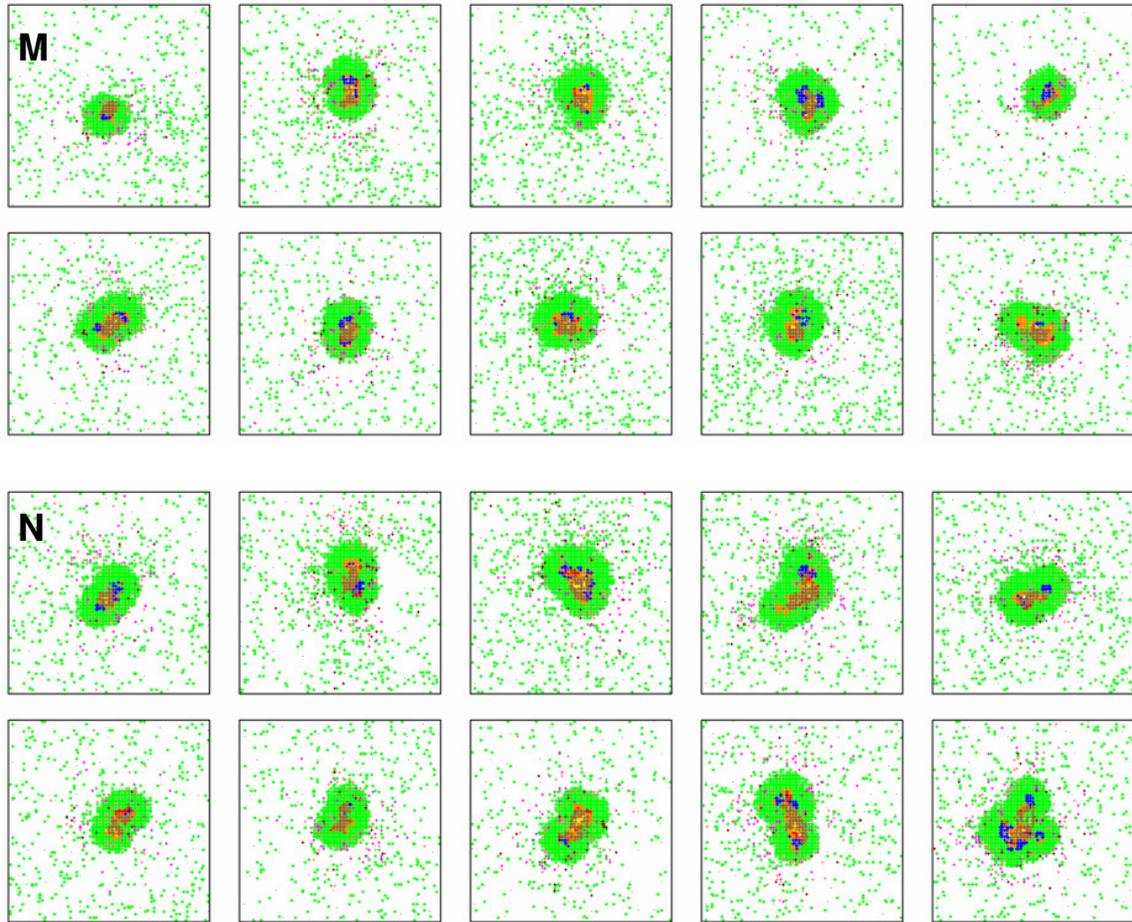


Figure S3 M-N. Deletion (M) and depletion (N) of TNF-induced immune cell recruitment, apoptosis and chemokine/TNF secretion from macrophages.

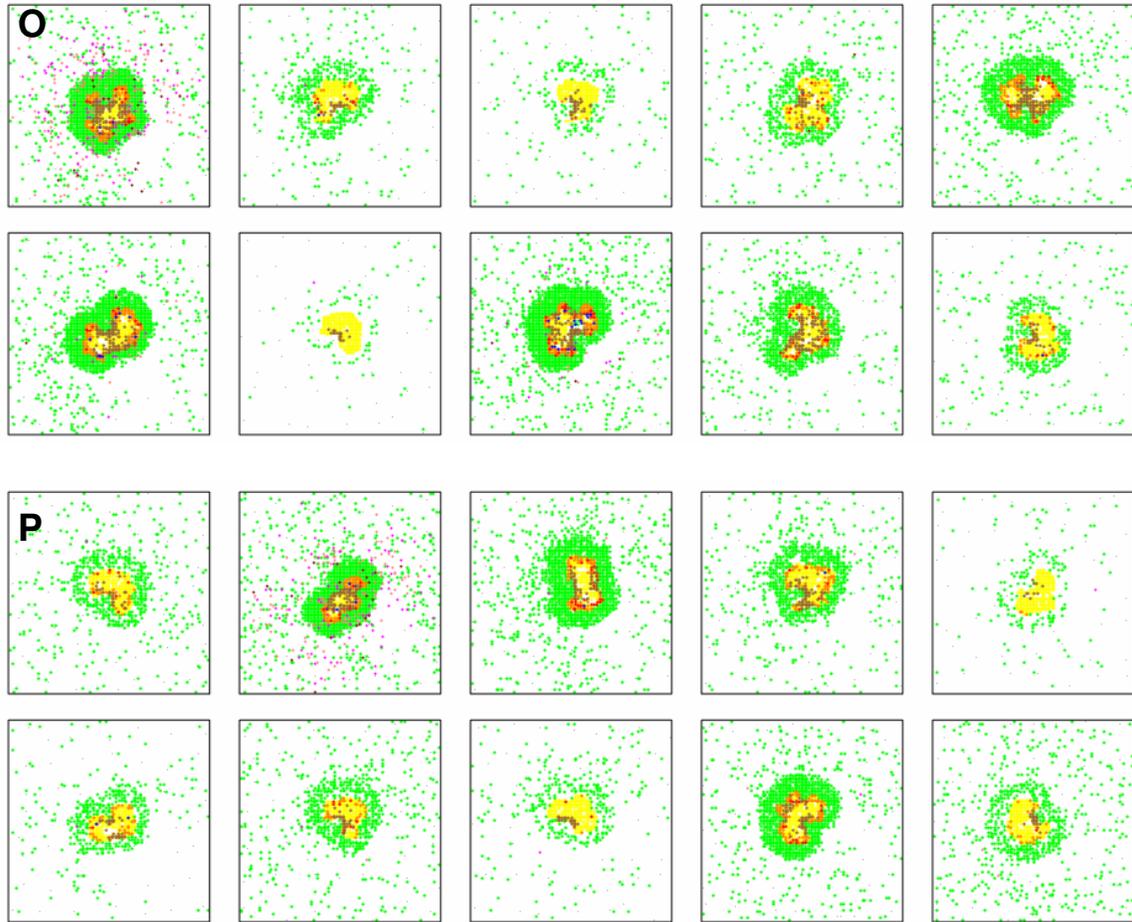


Figure S3 O-P. Deletion (O) and depletion (P) of TNF-induced macrophage activation, apoptosis and chemokine/TNF secretion from macrophages.