SUPPLEMENTARY METHODS AND TABLES

Drug transport from the blood into the lung tissue

To study the effect of TNF inhibitors on the immune response to Mtb, we first run the base model in the absence of TNF inhibitors by using a baseline set of parameter values that leads to stable control of infection (containment) in a granuloma as described in (1). After 100 days, at which time a well-circumscribed granuloma with stable bacterial levels ($<10^3$ total bacteria) forms, the granuloma is exposed to a TNF-neutralizing drug that enters the grid representing lung parenchyma via vascular sources, and diffuses among micro-compartments. The flux of a drug from a blood vessel into the tissue is related to the vascular permeability coefficient of the drug (k_c) and the drug gradient across the vessel wall by:

$$-D_{drug}\frac{\partial[Drug]}{\partial r}\Big|_{r=0} = k_c(C_p - [Drug]_{r=0}) \qquad (1)$$

where C_p is the concentration of the drug in blood, $[Drug]$ is the concentration of the drug in tissue that is a function of time and distance from the vessel (r), $[Drug]_{r=0}$ is the concentration of the drug at the outside wall of the vessel, and D_{drug} is drug diffusion coefficient in tissue. Using this equation and rearranging it for discrete-space flux on the 2-D grid gives:

$$C_{source} = C_{i,j} = \frac{\frac{1}{4}D_{drug}\{C_{i-1,j} + C_{i+1,j} + C_{i,j-1} + C_{i,j+1}\} + C_p k_c dx}{D_{drug} + k_c dx} \qquad (2)$$

where $C_{source} = C_{i,j}$ represents the drug concentration at the outside wall of the vascular source located at the micro-compartment (i,j) and dx = 20 μm is the lattice spacing through which diffusion occurs. Equation 2 implies that at very large vascular permeabilities ($k_c \rightarrow \infty$), $C_{i,j}$ tends to blood concentration of the drug (C_p). However, a zero permeability coefficient ($k_c = 0$) leads to $C_{i,j} = (1/4)\{C_{i-1,j} + C_{i+1,j} + C_{i,j-1} + C_{i,j+1}\}$ meaning that the drug flux from the blood vessel into the tissue becomes zero. Drug diffusion among micro-compartments on the grid with periodic boundary conditions occurs as described in (1).

TNF-neutralizing drugs differ in their dosing regimens and pharmacokinetic properties, including route of administration (intravenous versus subcutaneous), drug half-lives in plasma and the blood concentration peak-trough ratios. Etanercept and adalimumab are, for example, administered in frequent (weekly or bi-weekly) small subcutaneous doses that rapidly lead to smooth and uniform concentration-time profiles at steady state (2). This is consistent with assuming a constant blood concentration (C_p = constant) for these drugs in our model. However, infliximab is dosed every eight weeks in relatively large intravenous boluses that result in wide fluctuations in blood concentration of the drug (2, 3). To study the effect of these fluctuations on the function of a granuloma, we also simulate infliximab-mediated TNF neutralization in which blood concentration of infliximab follows a pharmacokinetic model ($C_p = f(\mathrm{t})$) presented by St Clair *et al* (4).

Neutralization of TNF by TNF inhibitors

Once TNF inhibitors penetrate from blood into the lung tissue, they can bind TNF and thus block TNF-mediated signaling in a granuloma. To analyze the effects of TNF-neutralizing drugs with various TNF binding properties, including TNF/drug association and dissociation kinetics, stoichiometry of binding as well as drug ability to bind mTNF versus sTNF on immunity to Mtb, we define three hypothetical classes of TNF inhibitors (Fig. 1C in the main text). These classes are defined based on TNF binding characteristics reported for human TNF-neutralizing drugs (including infliximab, adalimumab, etanercept and certolizumab) as described in Methods in the main text. An sTNF molecule with either one, two or three drug molecules bound is neutralized and not able to bind TNFR1 or TNFR2. This assumption is consistent with experimental data indicating that only trimeric TNF is biologically active and that both monomeric TNF and artificially prepared dimeric TNF do not efficiently trigger signaling in cells (5, 6). TNF/drug interactions for different classes of TNF inhibitors are modeled based on mass action kinetics. The reactions and equations are listed in Supplementary Table 2. These equations are solved in combination with TNF/TNFR kinetic equations from the base model.

TNF inhibitors with apoptotic and cytolytic activities

Some TNF inhibitors are reported to induce apoptosis or complement-dependent cytotoxicity (CDC) in TNF-expressing cells. This results from drug binding to mTNF and cross-linking of mTNF (7, 8). Based on descriptions presented for three classes of TNF

inhibitors, only a Class 3 TNF inhibitor has the potential to cross-link mTNF and mediate cell death.

We describe drug-induced cell death for each individual TNF-expressing cell (including infected, chronically infected and activated macrophages and T cells), as a Poisson process with a probability determined within each time-step (Δt), based on a Poisson rate parameter that is a function of the drug-induced death rate constant (k_{apopt}), the concentration of mTNF molecules that are bound to more than one drug molecule [mTNF/(drug)$_{>1}$], and the concentration threshold for [mTNF/(drug)$_{>1}$] for inducing apoptosis or CDC ($\tau_{death\text{-}Drug}$):

$$P_{death-Drug} = \begin{cases} 0 & ;\ [mTNF/(drug)_{>1}] < \tau_{death-Drug} \\ 1 - e^{-k_{apopt}([mTNF/(drug)_{>1}] - \tau_{death-Drug})\Delta t} & ;\ [mTNF/(drug)_{>1}] \geq \tau_{death-Drug} \end{cases} \quad (3)$$

This description for the drug-induced cell death is in line with the approach we used to describe TNF-induced apoptosis, one of the processes that serve as the link between the single-cell/molecular scale TNF/TNFR kinetics and the cellular/tissue scale dynamics in the baseline model (1). We assume that drug-induced death events, apoptosis and CDC, occur with equal chances. The difference between the consequences of apoptosis and CDC is only significant if the target cell is an infected or a chronically infected macrophage. Cell lysis as a result of CDC leads to the release of intracellular bacteria to the environment similarly to death due to age or bursting of a chronically infected macrophage as described in (1). However, drug-induced apoptosis, similarly to TNF-induced apoptosis, kills a fraction (we assume half) of intracellular bacteria (9).

Parameter estimation

We estimated values of the base model parameters, including ABM parameters, single-cell molecular scale TNF/TNFR kinetic parameters as well as TNF response (NF-κB activation and apoptosis) parameters based on available experimental data or via uncertainty analysis as described in (1). TNF inhibitor-associated parameter values are estimated based on literature data on human TNF-neutralizing drugs and are listed in Supplementary Table 1. Blood concentrations of TNF inhibitors are consistent with average steady state blood concentrations reported for human TNF-neutralizing drugs (C_p = constant) (2). When pharmacokinetic fluctuations of the concentration of a drug in blood is particularly of interest, we use $C_p = f(t)$; where $f(t)$ is the blood concentration-time profile as reported in literature for the drug.

Sensitivity analysis

When computational models include parameters describing a large number of known biological processes, it is critical to understand the role that each of these parameters plays in determining output. Sensitivity analysis is a technique to identify critical parameters of a model and quantify how input uncertainty impacts model outputs. Latin hypercube sampling (LHS) is an algorithm that allows multiple parameters to be varied and sampled simultaneously in a computationally efficient manner (10). We have previously used LHS sensitivity analysis as described in (1) to analyze the impact of base granuloma model parameter values on outputs, including bacterial and immune cell numbers, TNF concentration, granuloma size and caseation. Here, we use sensitivity

analysis to investigate whether the significance of the base model parameters in the presence of TNF inhibitors in the tissue differs from their significance in the absence of TNF inhibitors. We use base model parameter ranges as specified in (1) for sensitivity analysis. Results of sensitivity analysis will help us identify critical immune processes that impact granuloma function following anti-TNF treatments. The correlation of model outputs with each parameter is quantified via calculation of a partial rank correlation coefficient (PRCC). PRCC values vary between -1 (perfect negative correlation) and +1 (perfect positive correlation) and can be differentiated based on *p*-values derived from Student's *t* test. LHS simulations sampled each parameter 250 times. Each sampled parameter set was run twice and averages of the outputs were used to calculate PRCC values. The choice of the number of simulations is determined by the desired significance level for the PRCC (10, 11). Here, 250 runs imply that PRCC values above +0.24 or below -0.24 are significantly different from zero ($p < 0.001$).

Computer simulations and visualization

The model was implemented in C++. We use Qt, a C++ framework for developing cross-platform applications with a graphical user interface (GUI), to visualize and track different aspects of the granuloma, including the structure and molecular concentration gradients, as it forms and is maintained. Simulations can be run with or without graphical visualization. Simulations were run on Linux and Mac operating systems.

Supplementary Table 1: Model parameters associated with TNF neutralization reactions, definitions, and values.

Parameter	Parameter description	Value	Reference
D_{drug} (cm^2/s) *	Diffusion coefficient of drug	2.3×10^{-8}	(12, 13)
k_c (cm/s) †	Drug permeability in the lung tissue	1.1×10^{-8}-1.1×10^{-7}	(14)
C_p (M)	Blood concentration of the drug	1.25×10^{-8} (etanercept) 3.67×10^{-8} (adalimumab) 7.5×10^{-8} (infliximab)	(2)
$k_{on_TNF/Drug}$ ($M^{-1}s^{-1}$)	TNF/drug association rate constant	2.6×10^{5} (etanercept) 1.33×10^{5} (adalimumab) 5.7×10^{4} (infliximab)	(15, 16)
$k_{off_TNF/Drug}$ (s^{-1})	TNF/drug dissociation rate constant	1.3×10^{-3} (etanercept) 7.31×10^{-5} (adalimumab) 1.1×10^{-4} (infliximab)	(15, 16)
k_{deg_Drug} (s^{-1})	Drug degradation rate constant	1×10^{-6}	(3)
k_{deg} (s^{-1})	sTNF degradation rate constant	4.58×10^{-4}	(17)
k_{TACE} (s^{-1})	Rate constant for TNF release by TACE activity	4.4×10^{-4} (macrophages) 4.4×10^{-5} (T cells)	(18-22)
$k_{death\text{-}Drug} = k_{apopt}$ ($(\#/cell)^{-1}s^{-1}$)	Rate constant for drug-induced cell death and TNF-induced apoptosis	1.33×10^{-9}	Estimated (1)
$\tau_{death\text{-}Drug}$ (#/cell)	Concentration threshold for drug-induced cell death	5-80	Estimated

* Diffusion coefficient of the drug in tissue/granuloma was estimated in line with estimates for diffusible factors of similar molecular weight in tumors (12, 13).

† Drug permeability into lung tissue was estimated based on estimated tissue:blood concentration ratios for most antibodies reported to be in the range of 0.1-0.5 (14).

Supplementary Table 2: Definition of species involved in TNF neutralization, reactions, their rates (r_i) and model equations.

Membrane-bound reaction species		***Soluble reaction species***	
mTNF	Membrane-bound TNF	*sTNF*	Extracellular soluble TNF
$mTNF/(drug)_1$	1:1 mTNF/drug complex	*Drug*	TNF-neutralizing drug
$mTNF/(drug)_2$	1:2 mTNF/drug complex	$sTNF/(drug)_1$	1:1 sTNF/drug complex
$mTNF/(drug)_3$	1:3 mTNF/drug complex	$sTNF/(drug)_2$	1:2 sTNF/drug complex
		$sTNF/(drug)_3$	1:3 sTNF/drug complex

TNF neutralization reactions

	Reaction	Rate
1*	$mTNF + Drug \leftrightarrow mTNF/(drug)_1$	$r_1 = k_{on_TNF/Drug}[mTNF][Drug] - k_{off_TNF/Drug}[mTNF/(drug)_1]$
2†	$mTNF/(drug)_1 + Drug \leftrightarrow mTNF/(drug)_2$	$r_2 = k_{on_TNF/Drug}[mTNF/(drug)_1][Drug] - k_{off_TNF/Drug}[mTNF/(drug)_2]$
3	$mTNF/(drug)_2 + Drug \leftrightarrow mTNF/(drug)_3$	$r_3 = k_{on_TNF/Drug}[mTNF/(drug)_2][Drug] - k_{off_TNF/Drug}[mTNF/(drug)_3]$
4	$mTNF/(drug)_1 \rightarrow sTNF/(drug)_1$	$r_4 = k_{TACE}[mTNF/(drug)_1]$
5	$mTNF/(drug)_2 \rightarrow sTNF/(drug)_2$	$r_5 = k_{TACE}[mTNF/(drug)_2]$
6	$mTNF/(drug)_3 \rightarrow sTNF/(drug)_3$	$r_6 = k_{TACE}[mTNF/(drug)_3]$
7	$sTNF + Drug \leftrightarrow sTNF/(drug)_1$	$r_7 = k_{on_TNF/Drug}[sTNF][Drug] - k_{off_TNF/Drug}[sTNF/(drug)_1]$
8	$sTNF/(drug)_1 + Drug \leftrightarrow sTNF/(drug)_2$	$r_8 = k_{on_TNF/Drug}[sTNF][sTNF/(drug)_1] - k_{off_TNF/Drug}[sTNF/(drug)_2]$
9	$sTNF/(drug)_2 + Drug \leftrightarrow sTNF/(drug)_3$	$r_9 = k_{on_TNF/Drug}[sTNF][sTNF/(drug)_2] - k_{off_TNF/Drug}[sTNF/(drug)_3]$
10	$sTNF/(drug)_1 \rightarrow Drug$ *(sTNF degradation)*	$r_{10} = k_{deg}[sTNF/(drug)_1]$
11	$sTNF/(drug)_2 \rightarrow 2Drug$ *(sTNF degradation)*	$r_{11} = k_{deg}[sTNF/(drug)_2]$
12	$sTNF/(drug)_3 \rightarrow 3Drug$ *(sTNF degradation)*	$r_{12} = k_{deg}[sTNF/(drug)_3]$
13	$sTNF/(drug)_1 \rightarrow$ *degradation*	$r_{13} = k_{deg_Drug}[sTNF/(drug)_1]$
14	$sTNF/(drug)_2 \rightarrow$ *degradation*	$r_{14} = k_{deg_Drug}[sTNF/(drug)_2]$
15	$sTNF/(drug)_3 \rightarrow$ *degradation*	$r_{15} = k_{deg_Drug}[sTNF/(drug)_3]$
16	$Drug \rightarrow$ *degradation*	$r_{16} = k_{deg_Drug}[Drug]$

Model equations for TNF neutralization-associated reactions ‡

$$\frac{\partial [mTNF]}{\partial t} = -r_1$$

$$\frac{\partial [mTNF/(drug)_1]}{\partial t} = r_1 - r_2 - r_4$$

$$\frac{\partial [mTNF/(drug)_2]}{\partial t} = r_2 - r_3 - r_5$$

$$\frac{\partial [mTNF/(drug)_3]}{\partial t} = r_3 - r_6$$

$$\frac{\partial [sTNF]}{\partial t} = -r_7$$

$$\frac{\partial [sTNF/(drug)_1]}{\partial t} = (\frac{\rho}{N_{av}})r_4 + r_7 - r_8 - r_{10} - r_{13}$$

$$\frac{\partial [sTNF/(drug)_2]}{\partial t} = (\frac{\rho}{N_{av}})r_5 + r_8 - r_9 - r_{11} - r_{14}$$

$$\frac{\partial [sTNF/(drug)_3]}{\partial t} = (\frac{\rho}{N_{av}})r_6 + r_9 - r_{12} - r_{15}$$

$$\frac{\partial [Drug]}{\partial t} = -(\frac{\rho}{N_{av}})(r_1 + r_2 + r_3) - r_7 - r_8 - r_9 + r_{10} + 2r_{11} + 3r_{12} - r_{16}$$

* Drug binding to mTNF is only relevant to Class 2 and Class 3 TNF-neutralizing drugs.

† Sequential binding of drug to sTNF and mTNF is only relevant to Class 3 TNF neutralizing drugs.

‡ When a membrane-bound molecule releases to the extracellular space (i.e. the micro-compartment occupied by the cell), or when a soluble molecule binds to the cell membrane, a scaling factor (ρ/N_{av}) is required, where ρ is the cell density in the micro-compartment and can be computed as $(dx)^{-3}$ assuming that each micro-compartment is a cube of side dx, and N_{av} is the Avogadro's number.

Supplementary Table 3: PRCC values for the LHS sensitivity analysis of the effect of cellular/tissue scale and TNF-associated molecular scale parameters on model outcomes during treatment with etanercept at a permeability coefficient of $k_c = 1.1\times10^{-7}$ cm/s (Only parameters with significant PRCC values are indicated).

	Selected model outputs			
Model parameters	Total number of bacteria	Average sTNF concentration	Granuloma size	Caseation
δ_{chem}	+0.37	+0.35	+0.33	+0.33
T_{moveM}	-0.49	-0.50	-0.45	-0.37
$\tau_{recTgam}$	+0.44	+0.23		
T_{recr}				-0.29
α_{Bi}	+0.23	+0.24	+0.27	+0.57
δ_{TNF}				
$k_{synthMac}$	-0.51	-0.33	-0.39	
$k_{synthTcell}$			+0.27	
$k_{TACEMac}$				
K_{d1}		+0.30	+0.25	
k_{apop}				
$k_{NF\text{-}\kappa B}$	-0.32	-0.31	-0.29	-0.34
$\tau_{NF\text{-}\kappa B}$	+0.27	+0.21		+0.22

Supplementary Table 4: PRCC values for the LHS sensitivity analysis of the effect of cellular/tissue scale and TNF-associated molecular scale parameters on model outcomes during treatment with infliximab at a permeability coefficient of $k_c = 1.1\times10^{-7}$ cm/s (Only parameters with significant PRCC values are indicated).

	Selected model outputs			
Model parameters	Total number of bacteria	Average sTNF concentration	Granuloma size	Caseation
δ_{chem}	+0.34	+0.32	+0.32	+0.22
T_{moveM}	-0.36	-0.39	-0.37	+0.24
$\tau_{recTgam}$	+0.26	+0.27	+0.28	
T_{recr}				
α_{Bi}	+0.39	+0.36	+0.42	+0.55
δ_{TNF}				
$k_{synthMac}$	-0.49		-0.39	-0.37
$k_{synthTcell}$				
$k_{TACEMac}$	+0.24	+0.44	+0.32	+0.29
K_{d1}		+0.24		
k_{apop}	-0.27	-0.25	-0.24	-0.23
$k_{NF\text{-}\kappa B}$	-0.19			
$\tau_{NF\text{-}\kappa B}$				

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