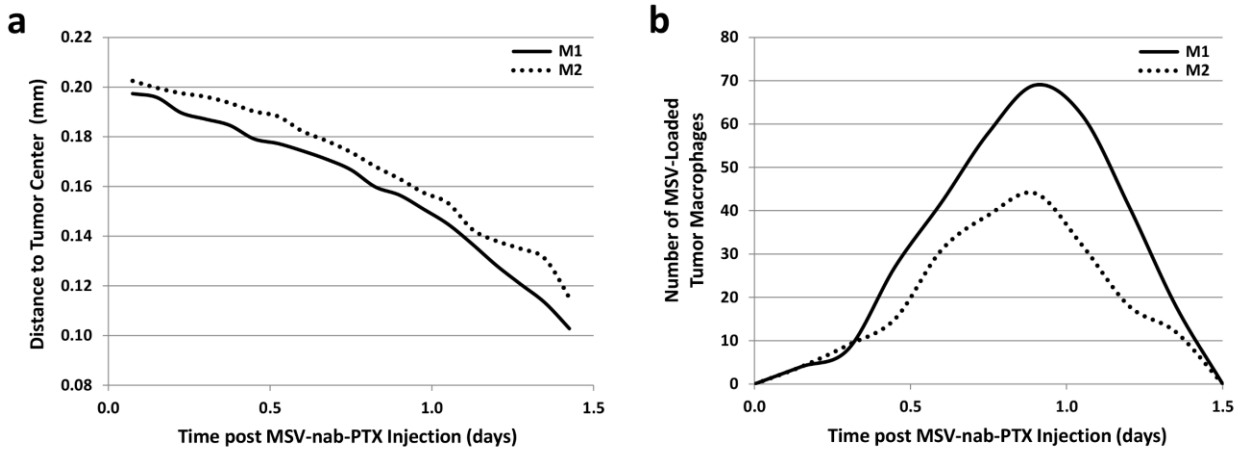
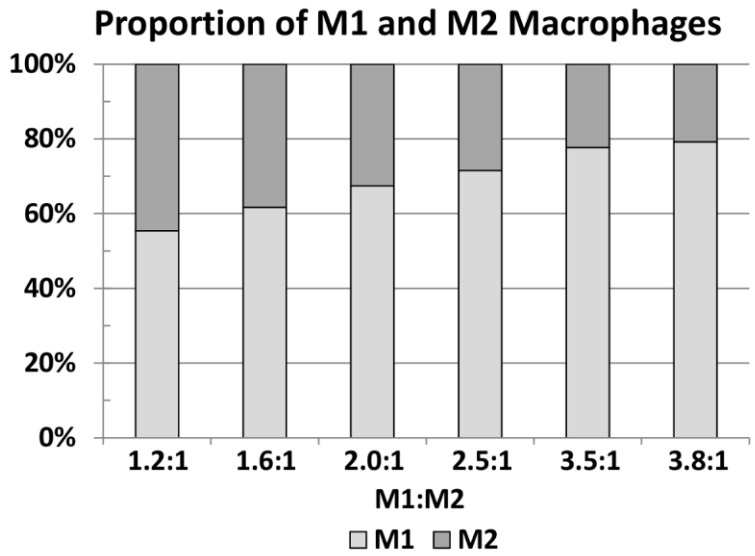
Supplementary Table 1. Main parameters of the computational model and their associated values. (*) Value is rescaled by the square of the simulation system characteristic length (1 cm) and divided by the system characteristic time (1 sec) multiplied by the oxygen diffusivity [1] (1 x 10^{-5} cm^2 s^{-1}).

Parameter	Value	Reference
Maximum tumor proliferation rate λ_M	1 day^{-1}	Measured *in vitro*
Tumor tissue threshold for hypoxia σ_H	0.5750	Calibrated to match 3D cell culture
Tumor tissue threshold for necrosis σ_N	0.5325	Calibrated to match 3D cell culture
Tumor native apoptosis rate λ_A	0 (*)	[2]
Tumor rate of volume loss in necrotic regions G_N	0.3 (*)	[2]
nab-PTX transfer rate from MSV-nab-PTX macrophages $\overline{\lambda}_{ev}^{s}$	5 (*)	[3]
nab-PTX diffusivity D_s	0.25 (*)	Estimated from experimental data
nab-PTX uptake rate by proliferating tumor cells λ^s	1.5 (*)	[3]
nab-PTX decay rate α	20 hr. half-life	[4]
MSV per MSV-nab-PTX macrophage	10	Measured *in vitro*
nab-PTX per MSV	0.0015 ng	Measured *in vitro*
Paclitaxel per nab-PTX molecule	10%	[4]
nab-PTX *in vitro* EC50 (48 hrs.) for 4T1 cells (monolayer)	125 ng/mL	Measured *in vitro*
Percentage of macrophages per tumor lesion total cells	10%	Measured *in vitro*
Resistance differential between monolayer and 3D cell culture when macrophages are present	1	Measured *in vitro*
Number of macrophages needed *in vivo* to attain EC50 *in vitro*	27,778 / mm^3	Calculated from experimental data
M1-induced death rate λ_{NO}	5 /s	Estimated from experimental data
M2 growth factor strength λ_F	1000 /s	Estimated from experimental data
nab-PTX -induced death effect $\overline{\lambda}_{effect}$	8275	Calibrated to match 3D cell culture
Diffusivity of agent affecting macrophage polarization (AAMP) D_N	0.25 (*)	Similar to nab-PTX
Release rate of AAMP from vasculature $\lambda_{release}^{N}$	0.5 (*)	Assumed half that of O_2
AAMP drug decay rate λ_{decay}^{N}	20 hr. half life	Similar to nab-PTX

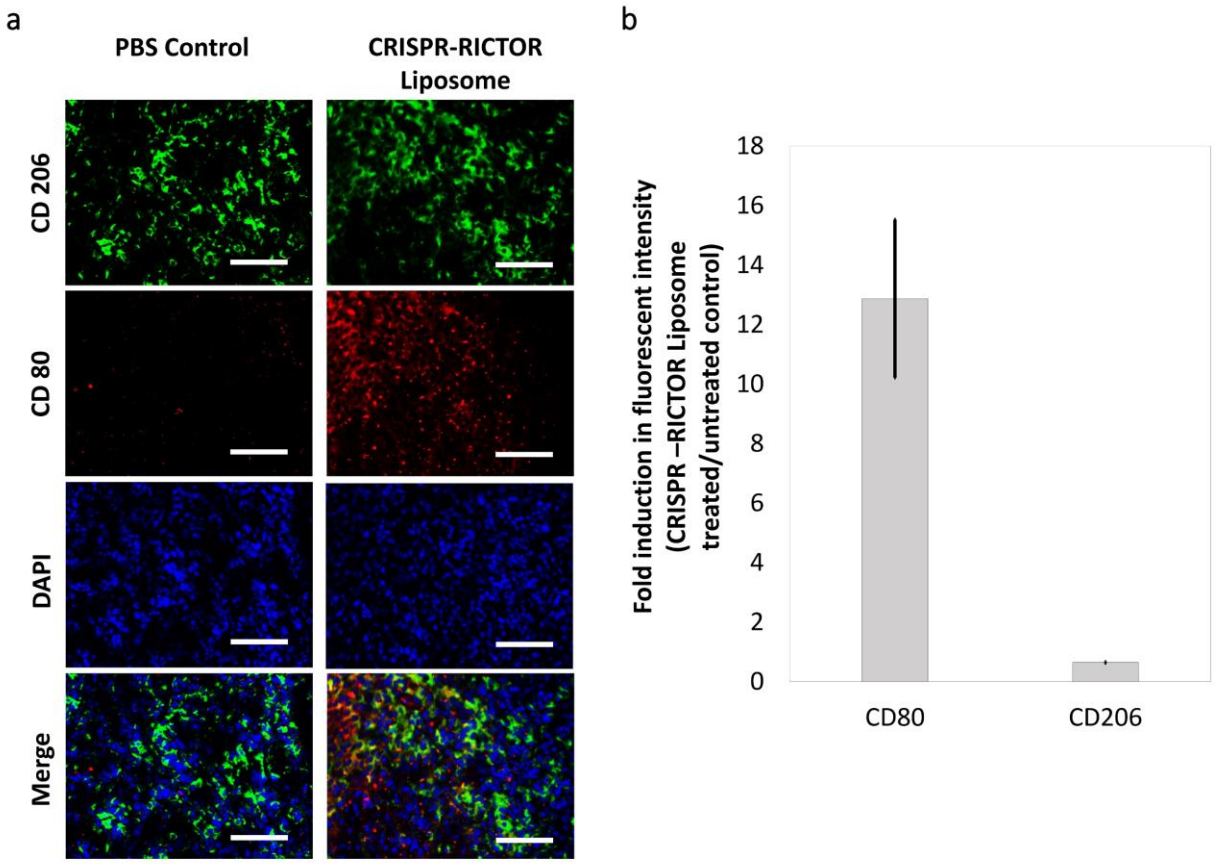
Supplementary Figures



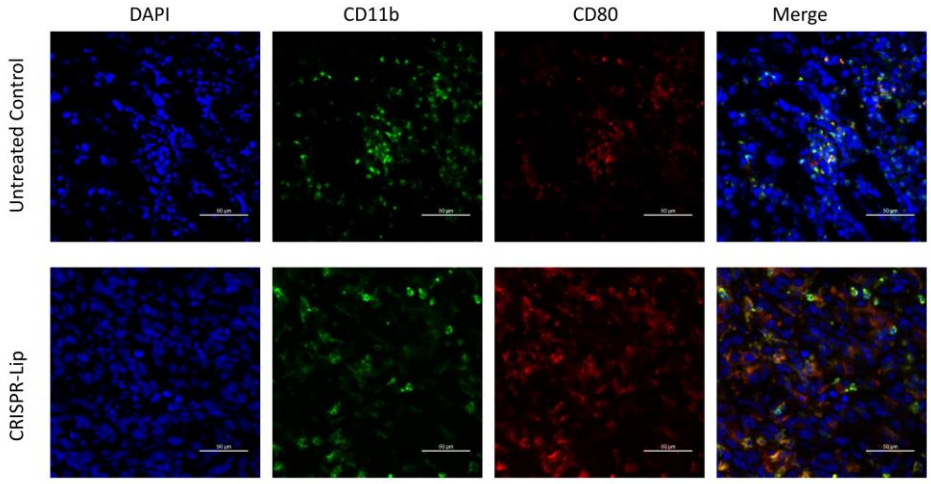
Supplementary Fig 1 Simulated tumor macrophage populations post systemic injection of MSV-nab-PTX. (a) Macrophage penetration and (b) number of MSV-nab-PTX loaded macrophages in a simulated breast cancer liver metastatic (BCLM) tumor lesion.



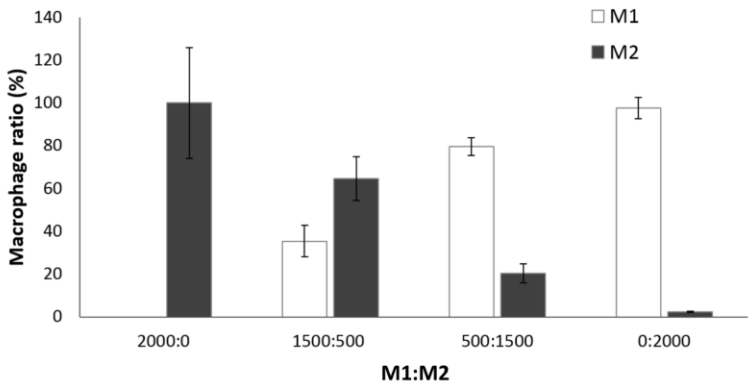
Supplementary Fig 2 Effect of a hypothetical "agent affecting macrophage polarization" (AAMP) on the simulated proportion of tumor-associated macrophages. An increasing ratio of M1 to M2 subtypes is achieved with increasing strength of the agent.



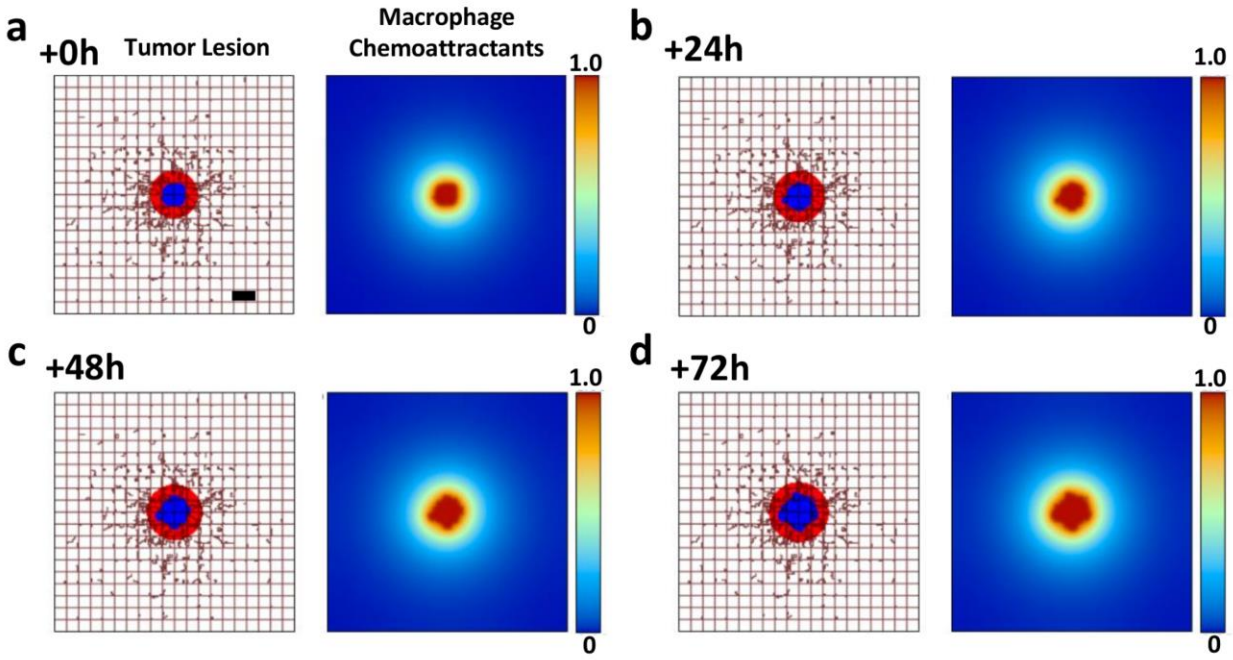
Supplementary Fig 3 Immunofluorescence analysis of 4T1 breast tumors 24h after CRISPR-RICTOR-Liposome treatment *in vivo* vs. untreated (injected with PBS) control. Tumors were stained for CD 80 (M1 marker) and CD206 (M2 marker) expression. (a) Immunofluorescence of tumor sections. (b) Quantification of CD80 and CD206 expression from histology. Mean±SD, n=6, scale bar=100µm.



Supplementary Fig 4 Immunofluorescence analysis of 4T1 tumors 24h after CRISPR-RICTOR-Liposome (CRISPR-Lip) treatment *in vivo* vs. Untreated (injected with PBS) control. To confirm that CD80 signal originates in macrophages of M1 phenotype, tumors were co-stained for CD80 (M1 marker, red) and CD11b (pan-macrophage marker, green). Scale bar=50µm.



Supplementary Fig 5 Phenotype of macrophages with different M1:M2 ratios cocultured with tumor spheroids was assessed after 48h. M1 macrophages were CRISPR-treated and differentiated in the presence of IFN-gamma/LPS, while M2 macrophages were polarized *in vitro* in the presence of IL-4/M-CSF. Macrophages were stained with CD80 antibody for M1 marker and with CD204 antibody for M2 marker. Staining signals were analyzed with NIS Elements and the ratios were calculated. Mean±SEM, biological replicates n=4.



Supplementary Fig 6 Simulation of a representative BCLM lesion. The lesion is shown growing over a period of 72h (a through d) with viable tumor tissue (red) enclosing a hypoxic region (blue) without necrosis. The dense liver capillary network is modeled by the rectangular grid (brown), with irregular sprouts generated through angiogenesis during the lesion progression. During this growth, macrophage chemoattractants (non-dimensional units) are increasingly released by the tumor cells into the surrounding microenvironment. Bar= 200 µm.

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