Detailed reactions and model equations for the manuscript titled 'Tumor microenvironment governs the prognostic landscape of immunotherapy for head and neck squamous cell carcinoma: A computational model-guided analysis'

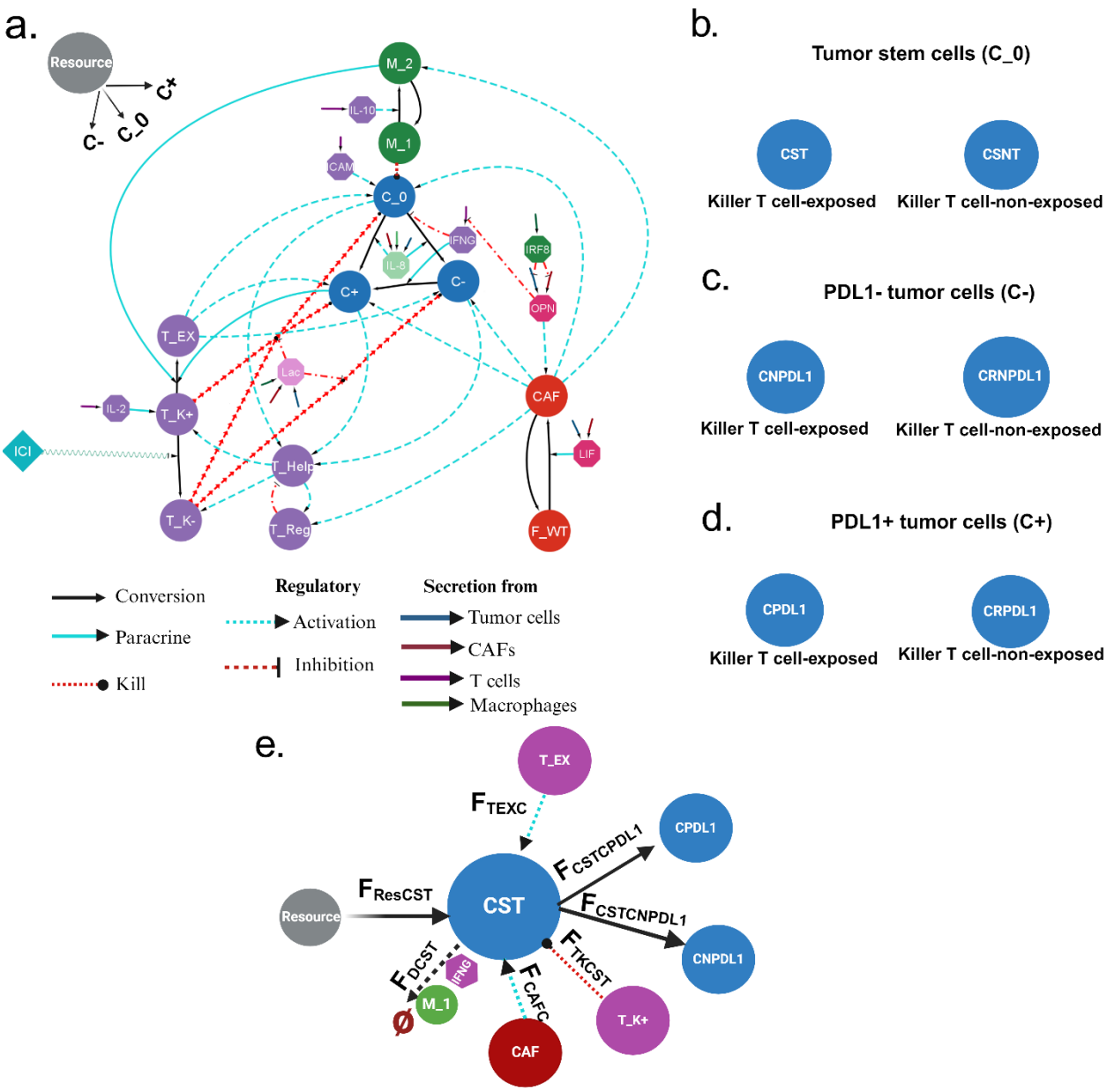

Figure S1. Detailed HNSCC TME network model: (a) The nodes are either the cell states or the molecular species, whereas the edges represent diverse forms of interactions. The acronyms C_0, C+, and C– refer to stem, PDL1+ (programed death ligand1), and PDL1– tumor cells, respectively. T_K+, T_K-, T_Help, T_Reg, and T_EX stands for PD1+ (programmed death 1), PD1- killer T cells, Helper T cells, Regulatory T cells, and Exhausted T cells, respectively.

M_1 and M_2 refer to macrophages of M1 and M2 phase, respectively. Further, F_WT and CAF correspond to wild type and invasive cancer associated fibroblasts, respectively. The acronyms IL-2, IL-8, IL-10 LIF, IFNG, IRF8, OPN, ICAM1, and Lac denote Interleukin 2, Interleukin 8, Interleukin 10, Leukemia Inhibitory Factor, Interferon Gamma, Interferon Regulatory Factor 8, Osteopontin, Intercellular Adhesion Molecule 1, and Lactate, respectively. All the cell states are assumed to be capable of self-proliferation and natural death. Therefore, the self-loops are not shown for brevity. **(b-d)** Each tumor cell state is subdivided depending on the accessibility from the Killer T cells. The Killer T cell-exposed tumor cells are exposed to immune response whereas the Killer T cell-non-exposed tumor cells are protected by the CAF-derived barrier from immune onslaught. **(e)** Flux-structure mapping for the killer T-cell-expose tumor stem cells.

Table S1: Mathematical representation of the fluxes corresponding to the HNSCC TME network in Figure S1.

Reaction flux	Mathematical expression
Proliferation of CST (F_{ResCST})	$ResK_{RCST}CST\left(1-\frac{CST}{(1-I_a)Y_{CST}+1}\right)\alpha_C$ $\alpha_C \coloneqq \frac{1}{a_{comp}(CPDL1+CNPDL1)+1}$ $I \coloneqq \tanh(\alpha K_{CAFB}CAF)$ α: Proportion of CAF engaged in barrier formation K_{CAFB}: Barrier formation rate
Exhausted T-cells-driven proliferation modulator of tumor cells (F_{TEXC})	$\left(1+K_{TXC}\frac{TEX}{TEX+1}\right)$
CAF-driven proliferation modulator of T-exposed Tumor cells (F_{CAFC})	$\left(1+K_{CAFC}\frac{CAF}{CAF+1}\right)$
Conversion from CST to CNPDL1($F_{CSTCNPDL1}$)	$K_{CSTCNPDL1}\left(\frac{IL8}{IL8+1}\right)CST$
Conversion from CST to CPDL1($F_{CSTCPDL1}$)	$K_{CSTCPDL1}\left(\frac{IL8}{IL8+1}\right)CST$
Killer T cell-driven elimination(F_{TKCST})	$K_{TKC}CST(TKPD1+TKNPD1)\gamma\beta$ $\gamma \coloneqq \frac{IFNG}{IFNG+1}$ $\beta \coloneqq \frac{1}{K_{LAC}LAC+1}$
Death of CST (F_{DCST})	$(K_{CSTD}+\delta_{IFNGCSTD}+\delta_{M1CSTD})CST$ $\delta_{IFNGCSTD} \coloneqq K_{IFNGCSTD}\frac{IFNG}{IFNG+1}$ $\delta_{M1CSTD} \coloneqq K_{M1CSTD}\frac{MACM1}{MACM1+1}$

Proliferation of CSNT ($F_{RESCSNT}$)	$$ResK_{RCSNT}CSNT\left(1-\frac{CSNT}{I_aY_{CST}+1}\right)\alpha_{C1}$$ $$\alpha_{C1} \coloneqq \frac{1}{\alpha_{comp}(CRNPDL1+CRPDL1)+1}$$
Exhausted T cell-driven proliferation for immune inaccessible tumor cells (F_{TEXCR})	$$\left(1+\alpha_T K_{TXC}\frac{TEX}{TEX+1}\right)$$ $$\alpha_T \coloneqq \exp(-\delta\alpha^2 CAF^2)$$ δ: Width of CAF barrier, α: proportion of CAF engaged in barrier forming
CAF-driven proliferation for immune inaccessible tumor cells (F_{CAFCR})	$$\left(1+K_{CAFCR}\frac{CAF}{CAF+1}\right)$$
Conversion from immune inaccessible stem to immune inaccessible tumor cells ($F_{CSNTCRNPDL1}$)	$$K_{CSNTCNPDL1}CSNT\frac{IL8}{IL8+1}$$
Conversion from immune inaccessible stem to immune inaccessible PDL1+ tumor cells ($F_{CSNTCRPDL1}$)	$$K_{CSNTCPDL1}CSNT\frac{IL8}{IL8+1}$$
Killer T cell-driven elimination of immune inaccessible tumor stem cell (F_{TKCSNT})	$$K_{TKC}\alpha_T(TKPD1+TKNPD1)CSNT\gamma\beta$$
Death of immune-inaccessible stem cells (F_{DCSNT})	$$F_{CSTD}\frac{CSNT}{CST}$$
Resource-driven growth of PDL1-immune-accessible tumor cells ($F_{RESCNPDL1}$)	$$ResK_{RCNPDL1}\gamma_{CNPDL1}CNPDL1\alpha_{C2}$$ $$\alpha_{C2}=\frac{1}{\alpha_{Comp}(CST+CPDL1)+1}$$ $$\gamma_{CNPDL1}=\left(1-\frac{CNPDL1}{(1-I_a)Y_{CNPDL1}+1}\right)$$

Killer T cell-driven elimination of PDL1- immune-accessible tumor cells ($F_{TKCNPDL1}$)	$K_{TKCNPDL1}CNPDL1(TKPD1 + TKNPD1)\gamma\beta$
Conversion from PDL1- to PDL1+ tumor cells ($F_{CNPDL1CPDL1}$)	$K_{CPDNPD}\frac{IFNG}{IFNG+1}CNPDL1$
Death of PDL1-, immune-accessible tumor cells ($F_{DCNPDL1}$)	$K_{CNPDL1D}CNPDL1$
Resource-driven growth of PDL1+, immune-accessible tumor cells ($F_{RESCPDL1}$)	$ResK_{RCPDL1}\gamma_{CPDL1}CPDL1\alpha_{C3}$ $\alpha_{C3} = \frac{1}{\alpha_{Comp}(CST + CNPDL1) + 1}$ $\gamma_{CPDL1} = \left(1 - \frac{CPDL1}{(1-I_a)Y_{CPDL1}+1}\right)$
Killer T cell-driven elimination of PDL1+ immune-accessible tumor cells($F_{TKNPDCPDL1}$)	$K_{TKCPDL1}CPDL1(TKNPD1)\gamma\beta$
Death of PDL1+, immune-accessible tumor cells (F_{DCPDL1})	$K_{CPDL1D}CPDL1$
Resource-driven growth of PDL1-, immune-inaccessible tumor cells ($F_{ResCRNPDL1}$)	$ResK_{RCRNPDL1}\gamma_{CRNPDL1}CRNPDL1\alpha_{C4}$ $\alpha_{C4} = \frac{1}{\alpha_{Comp}(CSNT + CRPDL1) + 1}$ $\gamma_{CRNPDL1} = \left(1 - \frac{CRNPDL1}{I_a Y_{CRNPDL1}+1}\right)$
Death of PDL1-, immune-inaccessible tumor cells ($F_{DCRNPDL1}$)	$K_{CNPDL1D}CRNPDL1$
Killer T cell-driven elimination of immune-inaccessible, PDL1- tumor cells ($F_{TKCRNPDL1}$)	$K_{TKC}CRNPDL1T_K\gamma\beta\alpha_T$ $T_K \coloneqq (TKPD1 + TKNPD1)$

IFNG-induced conversion to PDL1+ immune-inaccessible Tumor cells ($F_{CRNPDL1CRPDL1}$)	$K_{CPDNPD}\frac{IFNG}{IFNG+1}CRNPDL1$
Resource-driven growth of PDL1+, immune-inaccessible tumor cells ($F_{ResCRPDL1}$)	$ResK_{RCRPDL1}\gamma_{CRPDL1}CRPDL1\alpha_{C5}$ $\alpha_{C5}=\frac{1}{\alpha_{Comp}(CSNT+CRNPDL1)+1}$ $\gamma_{CRNPDL1}=\left(1-\frac{CRPDL1}{I_aY_{CRPDL1}+1}\right)$
Death of PDL1+, immune-inaccessible tumor cells ($F_{DCRPDL1}$)	$K_{CPDL1D}CRPDL1$
Proliferation of Killer PD1+ T cells ($F_{\mathrm{Pro}\,TKPD1}$)	$K_{TKPD}TKPD1\left(1-\frac{TKPD1}{Y_{TKM}-TEX-TKNPD1+1}\right)$
M1 macrophage, Helper-driven growth of Killer T cells ($F_{THTKPD1}$)	$1+K_{THTK}\frac{TH\ MACM1}{MACM1\ TH+1}$
IL2-driven growth of Killer T cells (F_{IL2TK})	$1+K_{IL2TK}\frac{IL2}{IL2+1}$
Effect of anti-PD1(u): Conversion from PD1+ to PD1- killer T cell($F_{TKPD1TKNPD1}$)	$K_{TKPDNPD1}TKPD1u$ u: Anti-PD1 dosage
Exhaustion rate ($F_{TKPD1TEX}$)	$K_{TKPDTEX}T_{KPD1}\frac{CPDL1\ MACM2}{CPDL1\ MACM2+1}$
Death rate of PD1+ killer T cell (F_{DTKPD1})	$K_{TKPDD}TKPD1$
Proliferation of PD1- Killer T cells($F_{\mathrm{Pro}\,TKNPD1}$)	$K_{TKNPD}TKNPD1\left(1-\frac{TKNPD1}{Y_{TKM}-TEX-TKPD1+1}\right)$

Helper-driven growth of Killer T cells $(F_{THTKNPD1})$	$1 + uK_{THTK}\frac{TH}{TH+1}$
Death rate of PD1-Killer T cells $(F_{DTKNPD1})$	$K_{TKPDD}TKNPD1$
Proliferation rate of helper T cells $(F_{\mathrm{Pro}\,TH})$	$K_{TH}\left(1-\frac{TH}{Y_{TH}}\right)$
Growth via antigen sensing (F_{CANTH})	$1 + K_{CANTH}\frac{(CNPDL1 + uCPDL1)}{(CNPDL1 + uCPDL1 + 1)}$
Regulator-driven inhibition (F_{TREGTH})	$\frac{1}{1 + K_{REGTH}TREG}$
Death of helper T cells (F_{DTH})	$K_{THD}TH$
Proliferation of regulatory T cells $(F_{\mathrm{Pro}\,TREG})$	$K_{TREG}TREG\left(1-\frac{TREG}{Y_{TREG}}\right)$
CAF-driven proliferation of Regulatory T cells $(F_{CAFTREG})$	$1 + K_{CAFTREG}\frac{CAF}{CAF+1}$
Death rate of Regulatory T cells (F_{DTREG})	$K_{TREGD}TREG$
Proliferation of exhausted T cells $(F_{\mathrm{Pro}\,TEX})$	$K_{TEX}TEX\left(1-\frac{TEX}{Y_{TKM}-TKNPD1-TKPD1+1}\right)$
Death rate of exhausted T cells (F_{DTEX})	$K_{TEXD}TEX$
Proliferation of wild-type fibroblasts $(F_{\mathrm{Pro}\,FWT})$	$K_{FWT}FWT\left(1-\frac{FWT}{Y_{FM}-CAF+1}\right)$

Conversion from wild type to invasive fibroblasts (F_{FWTCAF})	$K_{FWTCAF}\frac{(\alpha_{LIFFWT}\,LIF)^2}{(\alpha_{LIFFWT}\,LIF)^2+K_{LIFT}}FWT$ α_{LIFFWT}: Proportion of LIF in contact with FWT
Death of wild type fibroblasts (F_{DFWT})	$K_{FWTD}FWT$
Proliferation of invasive fibroblasts ($F_{\mathrm{Pr}oCAF}$)	$K_{CAF}CAF\left(1-\frac{CAF}{Y_{FM}-FWT+1}\right)$
OPN-induced growth of invasive fibroblasts (F_{OPNCAF})	$1+K_{OPNCAF}\frac{OPN}{OPN+1}$
M2 macrophage-induced growth (F_{M2CAF})	$1+K_{M2CAF}\frac{MACM2}{MACM2+1}$
Tumor cells-driven growth (F_{CANCAF})	$1+K_{CTCAF}\left(\frac{TUM_{AC}}{TUM_{AC}+1}+K_{CTCAFR}\frac{TUM_{IAC}}{TUM_{IAC}+1}\right)$ $TUM_{AC}\coloneqq(CST+CPDL1+CNPDL1)$ $TUM_{IAC}\coloneqq(CSNT+CRPDL1+CRNPDL1)$
Conversion from invasive to wild type fibroblasts (F_{CAFFWT})	$K_{CAFFWT}CAF$
Death of invasive fibroblasts (F_{DCAF})	$K_{CAFD}CAF$
Proliferation of M1-macrophages ($F_{\mathrm{Pr}oMACM1}$)	$K_{M1}MACM1\left(1-\frac{MACM1}{Y_{MM}-MACM2}\right)$
Proliferation of M1 macrophage via antigen-sensing ($F_{CANMACM1}$)	$1+K_{CANM1}\frac{(TUM_{PDL1-}+uTUM_{PDL1+})}{(TUM_{PDL1-}+uTUM_{PDL1+}+1)}$ $TUM_{PDL1-}\coloneqq(CST+CSNT+CNPDL1+CRNPDL1)$ $TUM_{PDL1+}\coloneqq(CPDL1+CRPDL1)$
Conversion from M1 to M2 macrophage (F_{M1M2})	$K_{M1M2}\frac{(\alpha_{IL10M1}IL10)^2}{(\alpha_{IL10M1}IL10)^2+1}$ $\alpha_{IL10M1}\coloneqq$ Proportion of IL-10 in contact with MACM1

Conversion from M2 to M1 macrophage (F_{M2M1})	$K_{M2M1}MACM2$
Death of M1 macrophage (F_{DMACM1})	$K_{M1D}MACM1$
Proliferation of M2 macrophage ($F_{\mathrm{Pr}oMACM2}$)	$K_{M2}MACM2\left(1-\frac{MACM2}{Y_{MM}-MACM1+1}\right)$
CAF-driven growth of M2 macrophage ($F_{CAFMACM2}$)	$K_{CAFM2}\frac{CAF}{CAF+1}$
Death of M2 macrophage (F_{DMACM2})	$K_{M2D}MACM2$
IL-2 secretion by Killer Cells (F_{TKIL2})	$K_{TKIL2}(TKPD1+TKNPD1)$
Degradation of IL-2 (F_{DIL2})	$K_{IL2D}IL2$
LIF secretion by CAF (F_{CAFLIF})	$K_{CAFLIF}CAF$
LIF secretion by Tumor cells (F_{CANLIF})	$K_{CANLIF}(TUM_{AC}+TUM_{IAC})$
Degradation of LIF (F_{DLIF})	$K_{LIFD}LIF$
IFNG secretion by T cells (F_{TKIFNG})	$K_{TIFNG}(TKPD1+TKNPD1)$
Inhibition of IFNG secretion by OPN ($F_{OPNIFNG}$)	$\frac{1}{\alpha_{OPNIFNG}OPN+1}$ $\alpha_{\mathrm{OPNIFNG}}$: Proportion of OPN in contact with IFNG

Degradation of IFNG (F_{DIFNG})	$K_{IFNGD}IFNG$
IL-8 secretion by M2 macrophage (F_{M2IL8})	$K_{M2IL8}MACM2$
IL8-secretion by CAF (F_{CAFIL8})	$K_{CAFIL8}CAF$
IL8-secretion by tumor cells (F_{CAFIL8})	$K_{CAFIL8}(TUM_{AC} + TUM_{IAC})$
Degradation of IL8 (F_{DIL8})	$K_{IL8D}IL8$
Lactate secretion by tumor cells (F_{CANLAC})	$K_{CANLAC}(TUM_{AC} + TUM_{IAC})$
Lactate secretion by M2 macrophage (F_{M2LAC})	$K_{M2LAC}MACM2$
Lactate degradation (F_{DLAC})	$K_{LACD}LAC$
IL10 secretion by Killer T cells (F_{TKIL10})	$K_{TKIL10}(TKPD1 + TKNPD1)$
Degradation of IL10 (F_{DIL10})	$K_{IL10D}IL10$
ICAM1 secretion by Killer T cells ($F_{TKICAM1}$)	$K_{TKICAM}(TKPD1 + TKNPD1)$
ICAM1 degradation (F_{DICAM1})	$K_{ICAM1}ICAM1$
OPN secretion by CAF (F_{CAFOPN})	$K_{CAFOPN}CAF$
OPN secretion by tumor cells (F_{CANOPN})	$K_{CANOPN}(TUM_{AC} + TUM_{IAC})$

Inhibition of OPN secretion by IRF8 ($F_{IRF8OPN}$)	$\frac{1}{\alpha_{IRF8OPN} IRF8 + 1}$ $\alpha_{\mathrm{IRF8OPN}}$: Proportion of IRF8 in contact with OPN
Degradation of OPN (F_{DOPN})	$K_{OPND} OPN$
IRF8 secretion by M1 macrophage (F_{M1IRF8})	$K_{M1IRF8} MACM1$
Degradation of IRF8 (F_{DIRF8})	$K_{IRF8D} IRF8$

Model equations: Given the fluxes in Table 1, we construct the overall mathematical model for the HNSCC TME.

$$\frac{dCST}{dt} = F_{RESCST}F_{TEXC}F_{CAFC} - F_{CSTCNPDL1} - F_{CSTCPDL1} - F_{TKCST} - F_{DCST}$$

$$\frac{dCSNT}{dt} = F_{RESCSNT}F_{TEXCR}F_{CAFCR} - F_{CSNTCRNPDL1} - F_{CSNTCRPDL1} - F_{TKCSNT} - F_{DCSNT}$$

$$\frac{dCNPDL1}{dt} = F_{RESCNPDL1}F_{TEXC}F_{CAFC} + F_{CSTCNPDL1} - F_{CNPDL1CPDL1} - F_{TKCNPDL1} - F_{DCNPDL1}$$

$$\frac{dCPDL1}{dt} = F_{RESCPDL1}F_{TEXC}F_{CAFC} + F_{CSTCPDL1} + F_{CNPDL1CPDL1} - F_{TKNPDCPDL1} - F_{DCPDL1}$$

$$\frac{dCRNPDL1}{dt} = F_{RESCRNPDL1}F_{TEXCR}F_{CAFCR} + F_{CSNTCRNPDL1} - F_{TKCRNPDL1} - F_{CRNPDL1CRPDL1} - F_{DCRNPDL1}$$

$$\frac{dCRPDL1}{dt} = F_{RESCRPDL1}F_{TEXCR}F_{CAFCR} + F_{CSNTCRPDL1} + F_{CRNPDL1CRPDL1} - F_{TKCRPDL1} - F_{DCRPDL1}$$

$$\frac{dRES}{dt} = K_{RIN}(Y_{RESM} - RES) - K_{RESD}RES$$

$$\frac{dTKPD1}{dt} = F_{ProTKPD1}F_{THTKPD1}F_{IL2TK} - F_{TKPD1TKNPD1} - F_{TKPD1TEX} - F_{DTKPD1}$$

$$\frac{dTKNPD1}{dt} = F_{ProTKNPD1}F_{THTKNPD1}F_{IL2TK} + F_{TKPD1TKNPD1} - F_{DTKNPD1}$$

$$\frac{dTH}{dt} = F_{ProTH}F_{CANTH}F_{TREGTH} - F_{DTH}$$

$$\frac{dTREG}{dt} = F_{ProTREG}F_{CAFTREG} - F_{DTREG}$$

$$\frac{dTEX}{dt} = F_{ProTEX}+F_{TKPD1TEX} - F_{DTEX}$$

$$\frac{dFWT}{dt} = F_{ProFWT} + F_{CAFFWT} - F_{FWTCAF} - F_{DFWT}$$

$$\frac{dCAF}{dt} = F_{ProCAF}F_{M2CAF}F_{CANCAF}F_{OPNCAF} + F_{FWTCAF} - F_{CAFFWT} - F_{DCAF}$$

$$\frac{dMACM1}{dt} = F_{ProMACM1}F_{CANMACM1} + F_{M2M1} - F_{M1M2} - F_{DMACM1}$$

$$\frac{dMACM2}{dt} = F_{ProMACM2}F_{CAFMACM2} + F_{M1M2} - F_{M2M1} - F_{DMACM2}$$

$$\frac{dIL2}{dt} = F_{TKIL2} - F_{DIL2} + C_{IL2}$$

$$\frac{dLIF}{dt} = F_{CANLIF} + F_{CAFLIF} - C_{LIFKO}LIF$$

$$\frac{dIFNG}{dt} = F_{TKIFNG}F_{OPNIFNG} - F_{DIFNG}$$

$$\frac{dIL8}{dt} = F_{CANIL8} + F_{CAFIL8} + F_{M2IL8} - F_{DIL8} - C_{IL8KO}IL8$$

$$\frac{dLAC}{dt} = F_{CANLAC} + F_{MACLAC} - F_{DLAC} - C_{LIFKO}LAC$$

$$\frac{dIL10}{dt} = F_{TKIL10} - F_{DIL10}$$

$$\frac{dICAM1}{dt} = F_{TKICAM1} - F_{DICAM1}$$

$$\frac{dOPN}{dt} = (F_{CANOPN} + F_{CAFOPN})F_{IRF8OPN} - F_{DOPN} - C_{OPNKO}OPN$$

$$\frac{dIRF8}{dt} = F_{MACM1IRF8} - F_{DIRF8}$$

Abbreviations

Res = Resource concentration

C_0 subtypes:
CST = Killer T cell-exposed Tumor stem cells
CSNT = Non-Killer T cell-exposed Tumor stem cells

C- subtypes:
CNPDL1 = Tumor cells exposed to Killer T cells without PDL-1
CRNPDL1 = Tumor cells hidden from Killer T cells without PDL-1

C+ subtypes:
CPDL1 = Tumor cells exposed to Killer T cells with PDL-1
CRPDL1 = Tumor cells hidden from Killer T cells with PDL-1

T cell subtypes:
TKPD1 = Killer T cells with PD-1 (TK+)
TKNPD1 = Killer T cells without PD-1 (TK-)
TH = Helper T cells
TREG = Regulatory T cells
TEX = Exhausted T cells

Fibroblast subtypes:
FWT = Wild type fibroblasts (F_WT)
CAF = Invasive cancer associated fibroblasts

Macrophage subtypes:
MACM1 = M1 phase macrophage
MACM2 = M2 phase macrophage

Molecular species:
IL2 = Interleukin 2
LIF = Leukemia inhibitory factor
IFNG = Interferon gamma
IL8 = Interleukin 8
LAC = Lactate
IL10 = Interleukin-10
OPN = Osteopontin
IRF8 = Interferon regulatory factor 8