**Supplementary Materials**

**Schematics of treatment dynamics**

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**Figure S1. Schematics of treatment dynamics.** (A) The model takes into account four tumor cell populations: Quiescent stem cells, Q, actively proliferating stem cells, S, transit amplifying cells, T, and differentiated cells, D. Actively dividing stem cells and transit amplifying cells divide at rates r1 and r2 respectively. With a probability p1, stem cell division results in two stem cells and with probability (1- p1) in two transit-amplifying cells (asymmetric division is discussed in the text). Similarly, the division of a transit amplifying cells results in two transit amplifying cells with probability p2. With a rate *f*, actively dividing stem cells enter quiescence, and quiescent stem cells become spontaneously activated with a rate *g.* Differentiated cells die at a rate *d*. Therapy is assumed to kill differentiated, transit amplifying, and tumor stem cells with rate c1, c2, and c3, respectively. In agreement with the notion that tumor stem cells are less sensitive to chemotherapy than differentiated or transit amplifying tumor cells, we assume that c3<<c1, c2. Negative feedback is not shown in the figure. (B) The chemotherapy-induced death of tumor cells triggers the release of wound-healing factors that promote the activation of quiescent tumor stem cells and their proliferation.

**Additional simulations for the spatial model**

Figure S2A exemplifies the effects of negative feedback on tumor size for untreated tumors. When the wound healing response is present, the tumor dynamics in response to treatment are similar to those in the non-spatial model. If the treatment-induced tumor stem cell death is a more dominant force compared to tumor stem cell repopulation, then after multiple treatment cycles, tumor load can be significantly lower compared to the untreated simulation (Figure 2SB). In contrast, if the rate of treatment-induced stem cell expansion/repopulation is more pronounced than the rate of stem cell death, treatment cycles could lead to post-therapy tumor sizes that are bigger than those occur without treatment (Figure 2SC) ­–the same behavior occurs for strong or no negative feedback; not shown. When negative feedback is present, there is a reduction in the treatment response over successive treatment cycles, even for a relative weak (k=0.2) negative feedback signal (Figure S2D).

 Finally, Figure S2E plots trajectories of tumor growth when no feedback is present. Note that there is an interesting difference between the treatment responses in the spatial and non-spatial models (compare Figures 2D and 2SF). In the non-spatial model each therapy round produces the same percent reduction in tumor size (Figure 2D). In the spatial model, on the other hand, there is a decrease in treatment response after multiple therapy rounds (Figure S2F). We recall that the killing of transit and differentiated cells during therapy can free up space for stem cells to divide. This process can lead to stem enrichment, which presumably is ultimately responsible for the decrease in chemotherapy sensitivity observed in the spatial model. (See the section on spatial growth in the main text.)

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**Figure S2. Spatial Model.** (A) Negative feedback and its effect on tumor growth without treatment. Dotted line: No feedback. Dashed line: Weak negative feedback. Solid line: Strong negative feedback. (B-D) Weak negative feedback (B) Tumor dynamics during five treatment cycles, indicated in grey. Black line: No treatment. Blue line: Treated tumor with wound-healing response (c3=0.01). (C) Same as panel B, but with a smaller stem cell death rate in response to chemotherapy (c3=0.001). (D) Percent of tumor reduction in each of the five treatment cycles depicted in panel C. (E-F) No negative feedback (E) Tumor dynamics during five treatment cycles. Red: Intact wound-healing response. Green: No wound-healing response (corresponding to celecoxib administration). Black: No treatment. (F) Percent of tumor reduction during each treatment cycle. Parameters were chosen as follows. Panel A: r1=r2=10; p1=0.65; p2=0.45; δ=0.0001; f=0.1; g=0.02; α=1; ε=1; η=0.02; β=0; c1=c2=c3=0 (no treatment). For strong feedback: h=0.5, k=1. For weak feedback h=0.5, k=0.2. For no feedback h=0. Panels B-D (weak feedback): r1=r2=10; p1=0.55; p2=0.45; δ=0.00025; f=0.1; g=0.01; α=1; ε=1; η=0.02; h=2; β=0.5; c1=c2=20, k=0.2 (in panel B, c3=0.01, in panel C, c3=0.001). Panels E-F (no feedback): r1=r2=10; p1=0.65; p2=0.45; δ=0.0001; f=0.5; g=0.1; α=1; ε=1; η=0.01; h=0; β=50; c1=c2=100;c3=0.001.

**Percent of the tumor killed in each treatment cycle**

In simulations for the non-spatial model the percent of the tumor that is removed during each treatment cycle does not change (**Figure 1E** in the manuscript). A mathematical motivation for this behavior is as follows. When treatment stops  in Equation (1) of the main text and consequently, the concentration of the wound-healing factor  decreases to zero exponentially fast. At this point, it is reasonable to consider the simpler system obtained by setting  in Equation 1. The resulting simplified system is a 4-dimensional linear homogeneous system of ODEs with constant coefficients and the following eigenvalues (note the plus/minus sign):



Given that all parameters are positive, , and , it follows that there is exactly one positive eigenvalue, while all the rest are negative. It is then trivial to verify that the ratio  converges exponentially fast to a constant that is independent of the initial conditions. In terms of the model this means that when treatment stops, the proportion of tumor stem cells quickly re-equilibrates to pre-treatment levels. Thus, with each treatment cycle, the degree to which the tumor responds to chemotherapy remains largely unchanged.

On the other hand, when feedback on the division rate is present, the percent of tumor stem cell increases with each treatment cycle, causing a decrease in tumor response to therapy over time. This behavior was verified numerically (See **Figure 3** and **Figure 4** in the main text, and **Figure** **S2** in this appendix). For an analytical proof that explains these dynamics for a related simpler system, the reader is referred to references [2] and [3] in the main text.