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THE ROLE OF THE CYTOKINES IL-27 AND IL-35 IN CANCER

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Abstract. The cancer-immune interaction is a fast growing field of research in biology, where the goal is to harness the immune system to fight cancer more effectively. In the present paper we review recent work of the interaction between T cells and cancer. $CD8^+$ T cells are activated by IL-27 cytokine and they kill tumor cells. Regulatory T cells produce IL-35 which promotes cancer cells by enhancing angiogenesis, and inhibit $CD8^+$ T cells via TGF-β production. Hence injections of IL-27 and anti-IL-35 are both potentially anti-tumor drugs. The models presented here are based on experimental mouse experiments, and their simulations agree with these experiments. The models are used to suggest effective schedules for drug treatment.

1. **Introduction.** The immune system may recognize tumor cells by their tumor specific antigen, and then try to kill them. But tumor cells may escape immune surveillance, and may even be able to exploit the immune systems to their own advantage. This is the case, for example, with regard to macrophages. Tumor cells in breast cancer attract macrophages by secreting M-CSF, and "educate" them to secrete VEGF, which promotes angiogenesis and tumor growth. But these tumor associated macrophages (TAMs) can be "re-educated" by a drug, such as GM-CSF, and then these cells will secrete sVEGF-R which blocks VEGF [8, 16, 17, 18, 53]. Macrophages appear in two polarized forms: poinflammatory macrophages (or classically activated macrophages) M_1, and anti-inflammatory macrophages (or alternatively activated macrophages) M_2. M_1 macrophages secrete a high level of proinflammatory cytokine IL-12, and a low level of anti-inflammatory cytokine IL-10, whereas M_2 macrophages secrete a low level of IL-12 and a high level of IL-10. IL-12 is an anti-tumor cytokine. Indeed, by cue from surface protein MHCII on macrophages, IL-12 activates $CD4^+$ T cells and indirectly (by IL-2 produced by $CD4^+$ T cells), also $CD8^+$ T cells, and $CD8^+$ T cells (also known as cytotoxic T cells, CTLs) kill cancer cells.

On the other hand, IL-10 produced by macrophages has been shown to block $CD8^+$ T cell activity. Hence it is in the interest of the tumor to polarize macrophages from M_1 to M_2. This indeed is what occurs, for example, in pancreatic cancer: The tumor secretes TGF-β and activates pancreatic stellate cells (PSCs) so that they also secrete TGF-β, as well as IL-6, and TGF-β and IL-6 polarizes M_1 into M_2 [37, 38, 42, 49].

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The IL-12 family includes four cytokines: IL-23, IL-12, IL-27, and IL-35. Although of similar structure, they have different proinflammatory/anti-inflammatory effects. In particular, they affect tumor in different ways. In Section 2 we describe general properties of these interleukins with regard to tumor growth, and in Sections 3 and 4 we focus on IL-27 and IL-35, respectively.

2. **The IL-12 family.** Interleukin 23 (IL-23) is a proinflammatory cytokine which plays a role in tumor progression by inducing inflammation in the tumor microenvironment [30]. However, whether this inflammation promotes or inhibits tumor growth depends on the specific tumor. IL-23 acts as anti-tumor agent in childhood B-acute lymphoblastic leukemia cells [10]. It has been shown to induce tumoral infiltration of $CD8^+$ T cells and to suppress tumor growth in pre-existing tumor mice [27]. IL-23 may also regulate metastatic prostate cancer [66]. On the other hand IL-23 promotes tumor growth in colon cancer [29]. It has also been shown that IL-23 and IL-12 play opposing roles in tumor growth [45, 55].

Interleukin-12 (IL-12) is a proinflammatory cytokine that plays a central role in the connection of the innate resistance and adaptive immunity by promoting Th1 and cytotoxic T lymphocyte activities, such as IFN-γ secretion. IL-12 could be a powerful therapeutic agent to eradicate tumor or to prevent the development of metastasis [4, 7, 14, 44]. However, IL-12 has also been shown to be excessively toxic [5, 39], In recent years there has been increasing interest to investigate the role of another member of the IL-12 family, namely, Interleukin-27 (IL-27), which is less toxic than IL-12, as a potential anti-tumor agent [23]. Since Hisada et al. [23] first reported on the anti-tumor efficacy of IL-27 in 2004, the potent anti-tumor activity of IL-27 has been verified in various tumor models [24, 52, 69]. Many studies suggest a role of IL-27 in enhancing anti-tumor $CD8^+$ T cell responses [9, 23, 47, 48, 68]. The enhancing role of IL-27 in generating anti-tumor CTL response was also demonstrated using IL-27R deficient mice [40, 50].

Interleukin 35 (IL-35) is the only member of the IL-12 family which is anti-inflammatory. IL-35 supports tumor growth by enhancing VEGF production by tumor cells [61], and by inducing differentiation of myeloid cells into myeloid derived suppressor cells (MDSCs) which inhibit $CD8^+$ T cells activation [43, 56, 57, 61]. IL-35 is also produced by regulatory T cells (T_{reg}s) in order to mediate the activities of toxic T cells [3, 36, 46, 61]. In summary, IL-27 is anti-cancer and could be used as therapeutic agent in cancer treatment, while IL-35 is pro-cancer so that anti-IL-35 could be a therapeutic agent in cancer treatment

3. **IL-27 and cancer.** In a recent study, Liu et al. [33] investigated the effect of IL-27 injection on plasmacytoma tumor in mice. They found that IL-27 significantly enhances the survival of activated tumor antigen specific $CD8^+$ T cells, and induces IL-10 upregulation in these T cells. It was also suggested in [33], and demonstrated in [19, 22, 41, 54], that CTL IL-10 production contributes to tumor rejection.

Liao et al. [31] developed a mathematical model based on the experiments of Liu et al. [33]. The model's network is shown in Fig. 1. We note that IL-10 can have inhibitory or stimulatory effect on cancer [21], but when produced by macrophages it mainly plays a negative role in tumor rejection [1, 26, 60]; here it is produced by $CD8^+$ T cells and plays anti-cancer role by increasing survival of these cells. We introduce the following variables:

$$I_{27}(r,t) \quad : \text{concentration of Interleukin-27 in } pg/cm^3,$$

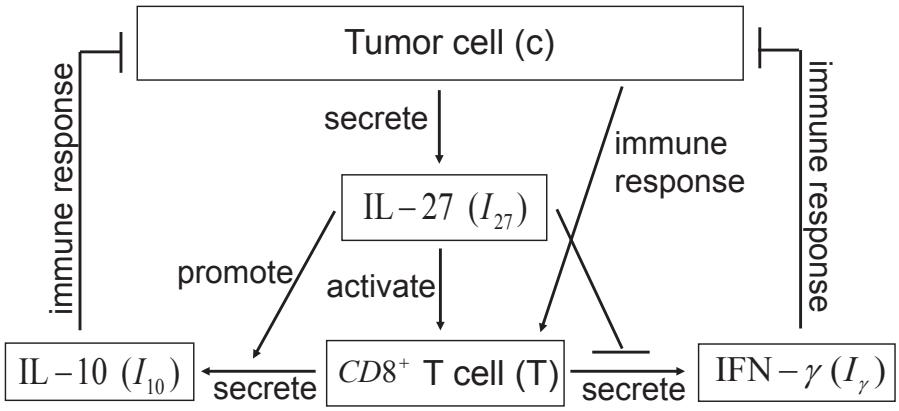

FIGURE 1. **A network of IL-27.** A network showing how IL-27 affects the immune response to tumor cells. $CD8^+$ T cells are activated by P1A antigen from tumor cells as well as by IL-27 which is secreted by tumor cells. Activated $CD8^+$ T cells secrete IFN-γ which is inhibited by IL-27, and IL-10 which is enhanced by IL-27. IL-10 and IFN-γ inhibit tumor cells.

$I_{10}(r,t)$: concentration of Interleukin-10 in pg/cm^3,
$T(r,t)$: (tumor antigen specific) activated $CD8^+$ T cell density, $cell/cm^3$,
$I_\gamma(r,t)$: concentration of Interferon-γ in pg/cm^3,
$c(r,t)$: tumor cell density, $cell/cm^3$

and consider the radially symmetric case, with the tumor environment being a ball $\{0 \le r < L\}$. Based on Fig. 1, the following system of PDEs was introduced in [31].

$$\begin{cases}
\frac{\partial I_{27}}{\partial t} = \underbrace{D_{I_{27}}\frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial I_{27}}{\partial r})}_{\text{diffusion}} + \underbrace{\alpha_{27}c}_{\text{production by tumor}} - \underbrace{\mu_{27}I_{27}}_{\text{degradation}} \\
\frac{\partial I_{10}}{\partial t} = \underbrace{D_{I_{10}}\frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial I_{10}}{\partial r})}_{\text{diffusion}} + \underbrace{s_{10}T}_{\text{production by CTL without } I_{27}} \\
\qquad + \underbrace{\alpha_{10}T\frac{I_{27}}{I_{27}+\sigma_{10}}}_{\text{production by CTL promoted by } I_{27}} - \underbrace{\mu_{10}I_{10}}_{\text{degradation}} \\
\frac{\partial T}{\partial t} = \underbrace{D_T\frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial T}{\partial r})}_{\text{diffusion}} + \underbrace{s_T\frac{c}{c+c_T}}_{\text{immune response}} - \underbrace{\frac{\mu_T}{1+\sigma_T I_{27}+\beta_T\sigma_T I_{10}}T}_{\text{pro-survival by } I_{27} \text{ and } I_{10}} \\
\frac{\partial I_\gamma}{\partial t} = \underbrace{D_\gamma\frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial I_\gamma}{\partial r})}_{\text{diffusion}} + \underbrace{\alpha_\gamma T\frac{s_\gamma}{s_\gamma+I_{27}}}_{\text{production by CTL inhibited by } I_{27}} - \underbrace{\mu_\gamma I_\gamma}_{\text{degradation}} \\
\frac{\partial c}{\partial t} = \underbrace{D_c\frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial c}{\partial r})}_{\text{diffusion}} + \underbrace{\lambda_1 c(1-\frac{c}{c_*})}_{\text{proliferation}} - \underbrace{\mu_c c}_{\text{death}} - \underbrace{\eta_c\frac{I_{10}}{I_{10}+\sigma_c}c}_{\text{inhibition by } I_{10}} - \underbrace{\eta_\gamma\frac{I_\gamma}{I_\gamma+s_c}c}_{\text{inhibition by IFN-}\gamma}.
\end{cases} \tag{3.1}$$

We note that in the experiments of Liu et al. [33], they used gene transfected tumor cells, J558-IL-27, to produce I_{27} in the tumor microenvironment. Accordingly, we

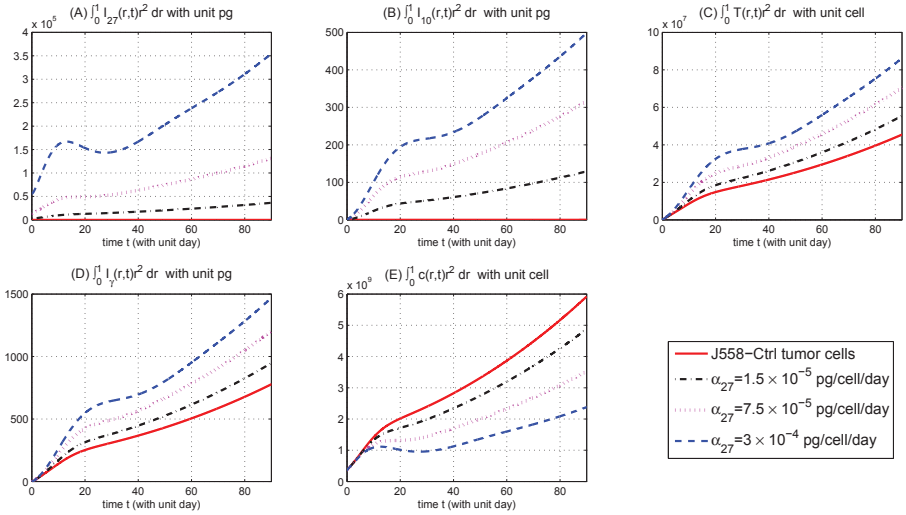

FIGURE 2. **Evolution of cells and cytokines for different production rates of IL-27.** (A), (B), (C), (D), and (E) are the profiles of total number of I_{27}, I_{10}, T, I_γ, and c, respectively, within 90 days. In (E), the curves displayed from top to bottom are for J558-Ctrl tumor cells, J558-IL-27 tumor cells with small ($\alpha_{27} = 1.5 \times 10^{-5}$ $pg/cell/day$), moderate ($\alpha_{27} = 7.5 \times 10^{-5}$ $pg/cell/day$), and large ($\alpha_{27} = 3 \times 10^{-4}$ $pg/cell/day$) production of IL-27, successively; $L = 1$ cm.

use the second term in the equation for I_{27} to represent the production of I_{27} by the transfected J558-IL-27 tumor cells. Fig. 2 shows that by increasing the production of IL-27 by cancer cells (i.e., by increasing α_{27}) the tumor total mass is decreased.

The parameters of the system (3.1) are listed in Table 1 together with their values; these values are taken from [31]. The simulation in Fig. 2 are in qualitative agreement with the experimental results in [33].

We conclude that injection IL-27 into the tumor may have benefits for cancer treatment. The administration of the IL-27 drug can be modeled by revising the equation for I_{27} as follows:

$$\frac{\partial I_{27}}{\partial t} = \underbrace{D_{I_{27}} \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial I_{27}}{\partial r}\right)}_{\text{diffusion}} + \underbrace{f(r,t)}_{\text{injection of } I_{27}} - \underbrace{\mu_{27} I_{27}}_{\text{degradation}}. \tag{3.2}$$

The function $f(r,t)$ is not a constant. We make the pharmacokinetic assumption that $f(r,t)$ decreases in r from the outer boundary of the tumor towards the inner core, and take

$$f(r,t) = F \times \frac{r^2 + a}{L^2 + a}, \tag{3.3}$$

where a is a positive constant; F is viewed as the "amount" of drug injection. The model was used in [31] to compare the efficacy of different protocols of injections of IL-27. Fig. 3 shows a comparison between continuous and intermittent injections: continuous injection is given a fixed amount F for 24 weeks, and the intermittent injection is given the amount $2F$ for three weeks with three weeks spacing between injection. The treatment ended after 24 weeks. We see that continuous injection has better efficacy in reducing the tumor burden, but the benefits of IL-27 treatment happen only while the treatment is ongoing; the treatment has neither short-term

TABLE 1. **Parameters for the IL-27 model.**

	Description	**Value with unit**
$D_{I_{27}}$	diffusion coefficient of I_{27}	$1.25 \times 10^{-3}\ cm^2/day$
α_{27}	production rate of I_{27} by tumor	$1.5 \times 10^{-5}\ pg/cell/day$
μ_{27}	degradation rate of I_{27}	$2/day$
$D_{I_{10}}$	diffusion coefficient of I_{10}	$1.25 \times 10^{-3}\ cm^2/day$
s_{10}	production rate from CTL without IL-27	$8.89 \times 10^{-8}\ pg/cell/day$
α_{10}	max production rate from CTL with IL-27	$1.128 \times 10^{-4}\ pg/cell/day$
σ_{10}		$5 \times 10^{3}\ pg/cm^3$
μ_{10}	degradation rate of I_{10}	$1.6 \times 10/day$
D_T	diffusion coefficient of CTL	$4.32 \times 10^{-6}\ cm^2/day$
s_T	production rate of CTL activated by tumor	$1.3968 \times 10^{8}\ cell/cm^3/day$
c_T		$5.76 \times 10^{10}\ cell/cm^3$
σ_T		$2 \times 10^{-4}\ pg/cm^3$
β_T		9
μ_T	death rate of CTL	$3 \times 10^{-1}/day$
D_γ	diffusion coefficient of I_γ	$1.25 \times 10^{-3}\ cm^2/day$
α_γ	max production rate of I_γ by CTL	$3.72 \times 10^{-5}\ pg/cell/day$
s_γ		$5 \times 10^{6}\ pg/cm^3$
μ_γ	degradation rate of I_γ	$2.16/day$
D_c	diffusion coefficient of tumor	$8.64 \times 10^{-6}\ cm^2/day$
λ_1	max proliferation rate	$4.68 \times 10^{-1}/day$
c_*		$10^{9}\ cell/cm^3$
μ_c	death rate of tumor	$1.73 \times 10^{-1}/day$
η_c	inhibition rate of tumor by I_{10}	$3.45 \times 10^{-1}/day$
σ_c		$1.5 \times 10^{2}\ pg/cm^3$
η_γ	inhibition rate of tumor by IFN-γ	$6 \times 10^{-1}/day$
s_c		$3 \times 10^{2}\ pg/cm^3$

benefits nor long term benefits after the drug has discontinued. Note that the growth rate of tumor is faster during the intermittent treatment "off" periods. This is due to the fact that the $CD8^+$ T cell population decreased as the tumor decreased during the treatment "on" periods. The faster growth rate of the tumor after the end of treatment brings it, at the end of week 30, to almost to the same level as the untreated tumor.

4. **IL-35 and cancer.** Interleukin-35 (IL-35) is produced by many human cancer tissues, including melanoma, B cell lymphoma, lung cancer, and colorectal cancer [35, 61, 67], and it plays important roles in tumor progression and tumor immune evasion [61]. $Fox3^+$ regulatory T cells (T_{reg}s) are common in tumor microenvironment [34, 63], where they induce immuno-suppression. They do so by producing various cytokines, including TGF-β, IL-10 [51], and IL-9 [15], thereby promoting tumor growth. It was also shown that T_{reg}s secrete IL-35 [6, 11, 12, 13, 58, 59, 64].

Recently Wang et al. [61] generated IL-35 producing plasmacytoma cancer cells (J558-IL-35) and compared them with "normal" plasmacytoma cancer cells (J558-Ctrl) to show that the expression of IL-35 in tumor microenvironment increased the number of myeloid derived suppressor cells (MDSCs), and promoted tumor angiogenesis; furthermore, IL-35 inhibited the infiltration of cytotoxic T lymphocytes into the tumor microenvironment and rendered the cancer cells less susceptible to CTL destruction.

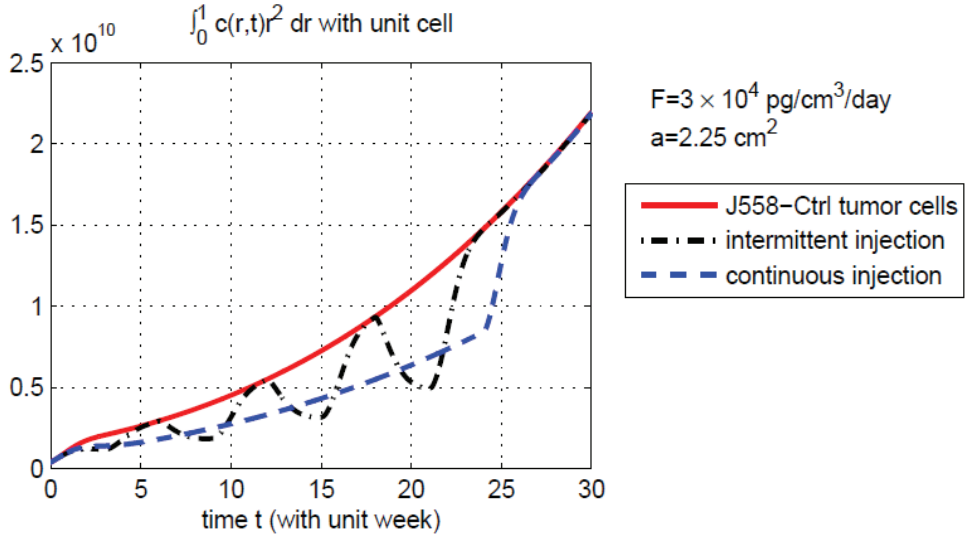

FIGURE 3. **Comparison of continuous versus intermittent treatment.** The upper curve is for J558-Ctrl tumor cells, the dotted-dashed curve $(- \cdot - \cdot -)$ is for intermittent injection, and the dashed curve is for continuous injection with $F = 3 \times 10^4\ pg/cm^3/day$ and $a = 2.25\ cm^2$, for the first 24 weeks.

These experimental results suggest that blocking IL-35 may be an effective therapeutic approach to human cancer. To explore this possibility , Liao et al. [32] developed a mathematical model based on the mice experiments of Wang et al. [61] which includes tumor cells, MDSCs, $CD8^+$ T cells, T_{reg}s, M-CSF, TGF-β, and IL-35, as well as VEGF, endothelial cells and oxygen, since IL-35 promotes angiogenesis. Fig. 4 displays the network introduced in [32]. Note that tumor cells attract MDSC which secretes TGF-β and IL-10 to promote T_{reg} [20, 65], and MDSC is also involved in a positive feedback loop

$$T_{reg} \rightarrow \text{IL-35} \rightarrow \text{MDSC} \rightarrow T_{reg},$$

where the last activation is mediated by TGF-β and IL-10. The presence of $CD8^+$ T cells was established experimentally in [61]. We hypothesize that their presence is due to MDSC. Indeed, MDSC secretes MCP-1 [2, 28] and MCP-1 attracts macrophages from the blood; macrophages then secrete IL-12 which activates $CD4^+$ T cells of class Th1 that in turn produce IL-2 which activates $CD8^+$ T cells. But MDSC also modulates the production of $CD8^+$ T cells via IL-10 production, and its pro-tumor activities enhance of IL-35 and VEGF.

Liao et al. [32] introduced a system of partial differential equations based on the network of Fig. 4, which included the following variables: $c(r,t)$ = tumor cell density, $q(r,t)$ = M-CSF concentration, $M(r,t)$ = Myeloid derived suppressor cell (MDSC) density, $I_{35}(r,t)$ = Interleukin-35 concentration, $R(r,t)$ = regulatory T cell density, $I_\beta(r,t)$ = TGF-β concentration, $T(r,t)$ = T cell density, $h(r,t)$ = VEGF concentration, $e(r,t)$ = endothelial cell density, $w(r,t)$ = oxygen concentration. They assumed that the tumor is radially symmetric and is contained in a sphere $0 \le r \le L$. The model equations in the nondimensional form are as follows:

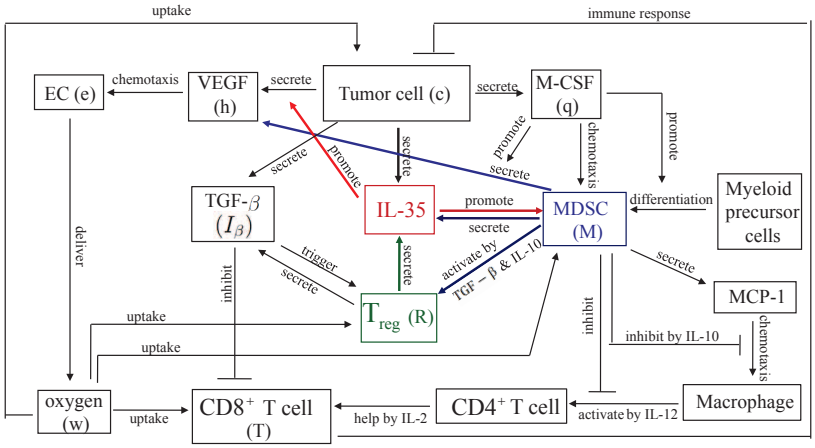

FIGURE 4. **A network showing how IL-35 promotes tumor growth.** M-CSF secreted by tumor cells promotes the differentiation of myeloid cells to MDSCs. M-CSF also attracts MDSCs to the tumor microenvironment by chemotaxis and promotes the secretion of VEGF by MDSCs. VEGF secreted by tumor cells and MDSCs attracts endothelial cells to trigger angiogenesis. IL-35 secreted by tumor cells, regulatory T cells and MDSCs promotes the secretion of VEGF by tumor cells and enhances the production of MDSCs. MDSCs promote T_{reg}s, but also secrete MCP-1 to attract macrophages into the tumor microenvironment. Macrophages secrete IL-12 to activate $CD4^+$ T cells, and $CD4^+$ T cells secrete IL-2 which activates $CD8^+$ T cells. MDSCs also produce large amount of IL-10, which inhibits the chemotaxis and activation of $CD4^+$ T cells.

$$\frac{\partial c}{\partial t} = \underbrace{D_c \frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial c}{\partial r})}_{\text{diffusion}} + \underbrace{\lambda_1(w)c(1-\frac{c}{c^*})}_{\text{proliferation}} - \underbrace{\lambda_2(w)c}_{\text{death by necrosis}} - \underbrace{\mu_c c}_{\text{apoptosis}} - \underbrace{\eta_c T c}_{\text{killed by T cell}}$$

$$\frac{\partial q}{\partial t} = \underbrace{D_q \frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial q}{\partial r})}_{\text{diffusion}} + \underbrace{\alpha_q c}_{\text{production by tumor}} - \underbrace{\mu_q q}_{\text{decay}}$$

$$\frac{\partial M}{\partial t} = \underbrace{\sigma_0}_{\text{source}} + \underbrace{\sigma_1 M_0 \times \frac{I_{35}}{I_{35}+c_M}}_{\text{induction of myeloid cells by } I_{35}} + \underbrace{D_M \frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial M}{\partial r})}_{\text{diffusion}} - \underbrace{\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 k_q M \frac{\partial q}{\partial r})}_{\text{chemotaxis by M-CSF}}$$
$$+ \underbrace{\alpha_M \frac{qM_0}{\sigma_M + q}}_{\text{differentiation from myeloid cells}} - \underbrace{\mu_M M}_{\text{death}}$$

$$\frac{\partial I_{35}}{\partial t} = \underbrace{D_{I_{35}} \frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial I_{35}}{\partial r})}_{\text{diffusion}} + \underbrace{\alpha_{35} c}_{\text{production by tumor}} + \underbrace{\beta_{35} R}_{\text{production by } T_{reg}} + \underbrace{\gamma_{35} M}_{\text{production by MDSC}}$$
$$\underbrace{-\mu_{35} I_{35}}_{\text{decay}}$$

$$\frac{\partial R}{\partial t} = \underbrace{D_R \frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial R}{\partial r})}_{\text{diffusion}} + \underbrace{\delta_M \frac{M}{M+\sigma_R}}_{\text{(indirect) activation by MDSC}} + \underbrace{\delta_\beta \frac{I_\beta}{I_\beta + \sigma_\beta}}_{\text{activation by TGF-}\beta} - \underbrace{\mu_R R}_{\text{death}}$$

$$\frac{\partial I_\beta}{\partial t} = \underbrace{D_\beta \frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial I_\beta}{\partial r})}_{\text{diffusion}} + \underbrace{\nu_c c}_{\text{production by tumor}} + \underbrace{\nu_R R}_{\text{production by } T_{reg}} - \underbrace{\mu_\beta I_\beta}_{\text{decay}}$$

$$
\begin{aligned}
\tfrac{\partial T}{\partial t} = {} & \underbrace{D_T \frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial T}{\partial r})}_{\text{diffusion}} + \underbrace{\frac{s_M}{s_M + a_1 M}}_{\text{inhibition}} \times [- \underbrace{\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 \beta_1 T \frac{\partial (a_2 M)}{\partial r})}_{\text{(indirect) chemotaxis by MCP-1}} \\
& + \underbrace{\frac{\beta_2 (a_3 M)}{(a_3 M) + c_5}}_{\text{(indirect) activation}} \times \underbrace{\frac{s_\beta}{s_\beta + I_\beta}}_{\text{inhibit by } I_\beta}] - \underbrace{\mu_T T}_{\text{death}} \\
\tfrac{\partial h}{\partial t} = {} & \underbrace{D_h \frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial h}{\partial r})}_{\text{diffusion}} + \underbrace{\lambda_5(w) c \times \frac{I_{35} + k_1}{I_{35} + \sigma_h}}_{\text{production by tumor promoted by } I_{35}} + \underbrace{\lambda_6(w) M \times \frac{q + k_2}{q + 1}}_{\text{production by MDSC}} - \underbrace{\mu_h h}_{\text{decay}} \\
\tfrac{\partial e}{\partial t} = {} & \underbrace{D_e \frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial e}{\partial r})}_{\text{diffusion}} - \underbrace{\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 k_h e \frac{\partial h}{\partial r})}_{\text{chemotaxis by VEGF}} + \underbrace{\lambda_{12} e (1 - \frac{e}{e_1})(h - h_1) H(h - h_1)}_{\text{proliferation}} \\
\tfrac{\partial w}{\partial t} = {} & \underbrace{\lambda_7 e}_{\text{delivered by EC}} + \underbrace{D_w \frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial w}{\partial r})}_{\text{diffusion}} - \underbrace{\lambda_8 T w}_{\text{uptake by CD8}^+ \text{ T cell}} - \underbrace{\lambda_9 M w}_{\text{uptake by MDSC}} \\
& - \underbrace{\lambda_{10} R w}_{\text{uptake by T}_{\text{reg}}} - \underbrace{\lambda_{11} c w}_{\text{uptake by tumor}} .
\end{aligned}
\tag{4.1}
$$

Wang et al. [61] used gene transfected tumor cells, J558-IL-35, to produce I_{35} in the tumor microenvironment, in addition to the IL-35 which is secreted by T_{reg}s. Accordingly, Liao et al. varied the parameter value of α_{35} such that $\alpha_{35}c > \beta_{35}R > \gamma_{35}M$ for gene transfected J558-IL-35 cancer cells and $\beta_{35}R > \gamma_{35}M > \alpha_{35}c$ for (wild type) J558-Ctrl cancer cells. Fig. 5 displays the simulation results in [32]; as it is seen, they agree quantitatively with the measurements reported in Wang et al. [61].

The parameters of the system (4.1) are listed in Tables 2 and 3 together with their values; these values are taken from [32]. We note that we have introduced in this model all the variables that were measured in [61], namely, c (cancer cells), M (MDSC), I_{35}, R (T_{reg}), T ($CD8^+$) and h (VEGF) so that we could compare the model simulations with the experimental data in [61]. In addition we introduced the most essential quantities that make connections among the above variables, namely, q (M-CSF), e (endothelial cells) and w (oxygen). In this sense the model, although quite complex, is minimal.

Next, Liao et al. [32] introduced the effect of anti-IL-35 drug, which inhibits the production of IL-35, into the model by modifying the equation for I_{35} as follows:

$$
\begin{aligned}
\frac{\partial I_{35}}{\partial t} = {} & \underbrace{D_{I_{35}} \frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial I_{35}}{\partial r})}_{\text{diffusion}} + \frac{1}{f(r,t)}[\underbrace{\alpha_{35} c}_{\text{production by tumor}} \\
& + \underbrace{\beta_{35} R}_{\text{production by T}_{\text{reg}}} + \underbrace{\gamma_{35} M}_{\text{production by MDSC}}] - \underbrace{\mu_{35} I_{35}}_{\text{decay}},
\end{aligned}
\tag{4.2}
$$

where $f(r,t)$ is taken to be as in (3.3).

Fig. 6 shows the simulation results in [32] for continuous and intermittent protocols of administering the drug, under different production rates α_{35}, with fixed total amount of drug. As it is seen, administering the drug continuously at fixed amount yields better results than every alternate week at twice the amount They also found that the percentage of tumor reduction under anti-IL-35 drug improves

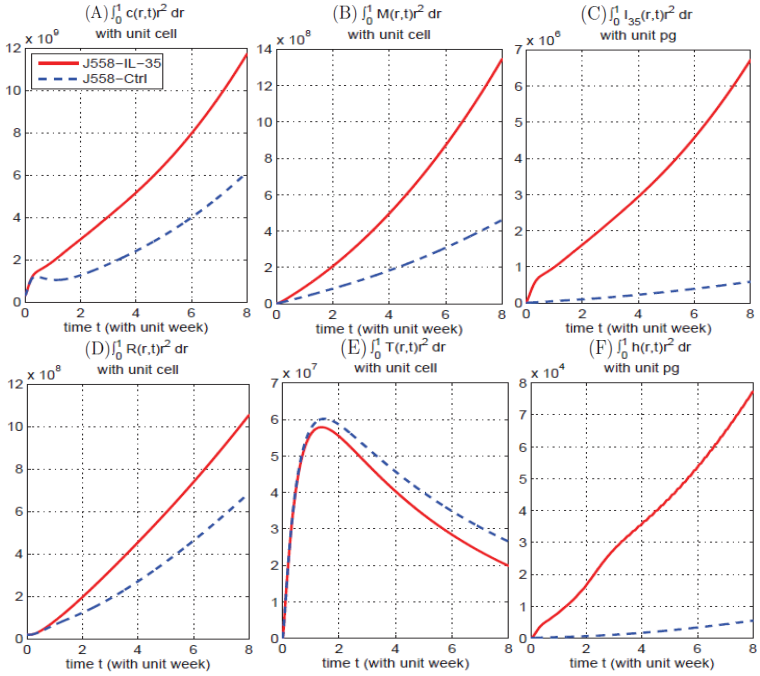

FIGURE 5. **Evolution of cells and cytokines for J558-IL-35 and J558-Ctrl mice models.** Panels (A) to (F) show the profiles of the total numbers of tumor cells, MDSCs, I_{35}, T_{reg}s, $CD8^+$ T cells, and VEGF for J558-IL-35 tumor cells with large I_{35} production (solid curve) and J558-Ctrl tumor cells (dashed curve).

when the production of IL-35 by cancer is increased, as in fact was reported in lung and colorectal cancers [35, 67].

5. **Conclusion.** In this paper we reviewed some recent papers on the interaction between interleukines IL-27 and IL-35 (both from the IL-12 family) and cancer; IL-27 is anti-cancer and IL-35 is pro-cancer. We presented mathematical models by systems of partial differential equations, based on *in vivo* mice experiments. The model simulations agree quantitatively with the experimental results. The models were used to determine how drugs can be administrated (continuously or intermittently) in order the better reduce tumor growth. However, our conclusions should be viewed as hypotheses to be tested experimentally.

The model simulations in Sections 3 and 4 are in agreement with experimental results [33, 61]. It would be interesting to explore the competing nature of IL-27 and IL-35. While IL-27 is a drug injected externally into the tumor, IL-35 is produced intrinsically by $T_{reg}s$. In the experiments in [33] only $CD8^+$ T cells were considered, but IL-27 is known to activate also Th1 cells and regulatory T cells [25, 62]. It would be interesting to model the interaction between tumor cells and all these T cells under IL-27 injection, that will include the various cytokines produced by the T cells (e.g. TGF-β, IL-10, IL-12, IFN-γ), including IL-35.

TABLE 2. **Parameters for the IL-35 model.**

	Description	Dimensional
D_c	Diffusion coefficient of tumor cells	$4.32 \times 10^{-6}\ cm^2/day$
c^*	Carrying capacity of tumor cells	$10^9\ cell/cm^3$
μ_c	Apoptosis rate of tumor cell	$4.15 \times 10^{-1}/day$
η_c	Killing rate of tumor cells from T cells	$3.1574 \times 10^{-6} cm^3/cell/day$
λ_1	Maximal proliferation rate of tumor cells	$2.5/day$
λ_2	Maximal necrosis rate of tumor cells	$8.3 \times 10^{-1}/day$
w_n	Oxygen lower bound in necrotic	$3.57 \times 10^7\ pg/cm^3$
w_h	Oxygen lower bound in extremely hypoxic	$10^8\ pg/cm^3$
w_0	Normal oxygen level	$4.65 \times 10^8\ pg/cm^3$
D_q	Diffusion coefficient of M-CSF	$1.728 \times 10^{-1}\ cm^2/day$
α_q	Production rate of M-CSF by tumor cell	$2.7648 \times 10^{-5}\ pg/cell/day$
μ_q	Decay rate of M-CSF	$4.1472/day$
σ_0	Source of MDSC	$1.10345 \times 10^5\ cell/cm^3/day$
σ_1	Maximal production rate via I_{35}	$4.65518 \times 10^2/day$
c_M		$10^5\ pg/cm^3$
D_M	Diffusion coefficient of MDSC	$4.32 \times 10^{-6}\ cm^2/day$
k_q	Chemotaxis rate of MDSC for M-CSF	$5.2 \times 10^{-7}\ cm^5/pg/day$
α_M	Polarization rate of MDSC by M-CSF	$7.5 \times 10^{-1}/day$
M_0	Density of myeloid precursor cells	$8 \times 10^3\ cell/cm^3$
σ_M		$7.5 \times 10\ pg/cm^3$
μ_M	Death rate of MDSC	$3 \times 10^{-2}/day$
$D_{I_{35}}$	Diffusion coefficient of I_{35}	$1.25 \times 10^{-3}\ cm^2/day$
α_{35}	I_{35} production rate by tumor for J558-IL-35	$10^{-3}\ pg/cell/day$
α_{35}	I_{35} production rate by tumor for J558-Ctrl	$10^{-7} pg/cell/day$
β_{35}	Production rate of I_{35} from T_{reg}	$1.67 \times 10^{-3}\ pg/cell/day$
γ_{35}	Production rate of I_{35} from MDSC	$10^{-4}\ pg/cell/day$
μ_{35}	Decay rate of I_{35}	$2/day$
D_R	Diffusion coefficient of T_{reg}	$4.32 \times 10^{-6}\ cm^2/day$
δ_M	Maximal activation rate of T_{reg} by MDSC	$1.25 \times 10^6\ cell/cm^3/day$
σ_R		$10^7\ cell/cm^3$
δ_β	Maximal activation rate of T_{reg} by TGF-β	$3.327 \times 10^6\ cell/cm^3/day$
σ_β		$2.4 \times 10^3\ pg/cm^3$
μ_R	Death rate of T_{reg}	$10^{-1}/day$

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TABLE 3. **Parameters for the IL-35 model.**

	Description	Dimensional
D_β	Diffusion coefficient of I_β	$8.64 \times 10^{-2}\ cm^2/day$
ν_c	Production rate of I_β by tumor cells	$5.5 \times 10^{-6}\ pg/cell/day$
ν_R	Production rate of I_β by T_{reg}s	$9 \times 10^{-7}\ pg/cell/day$
μ_β	Decay rate of I_β	$0.693/day$
D_T	Diffusion coefficient of T cells	$4.32 \times 10^{-6}\ cm^2/day$
s_M		$5 \times 10^6\ pg/cm^3$
β_1	Chemotaxis rate of T cell from MCP-1	$8.64 \times 10^{-9}\ cm^5/pg/day$
β_2	Activation rate from IL-12	$2.5 \times 10^5\ cell/cm^3/day$
a_1	Production rate of IL-10 by MDSC	$2\ pg/cell$
a_2	Chemotaxis rate of MCP-1 by MDSC	$10^{-2}\ pg/cell$
a_3	Production rate of IL-12 by MDSC	$10^{-2}\ pg/cell$
c_5		$7.5 \times 10\ pg/cm^3$
s_β		$2.9 \times 10^3\ pg/cm^3$
μ_T	Death rate of T cells	$3 \times 10^{-1}/day$
D_h	Diffusion coefficient of VEGF	$8.64 \times 10^{-2}\ cm^2/day$
k_1		$3.7 \times 10^2\ pg/cm^3$
σ_h	Critical value of I_{35}	$3.7 \times 10^5\ pg/cm^3$
q_0	Critical value of M-CSF	$10^3\ pg/cm^3$
k_2		$q_0/100 = 10\ pg/cm^3$
μ_h	Decay rate of VEGF	$1.08864 \times 10/day$
λ_5		$2.86 \times 10^{-4}\ pg/cell/day$
λ_6		$1.58 \times 10^{-3}\ pg/cell/day$
w^*		$4.185 \times 10^8\ pg/cm^3$
D_e	Diffusion coefficient of EC	$4.32 \times 10^{-6}\ cm^2/day$
k_h	Chemotaxis force of EC by VEGF	$4.1472 \times 10^{-7}\ cm^5/pg/day$
λ_{12}	Proliferation rate by VEGF	$5.83 \times 10^{-1}/day$
e_1	Maximal density of EC inside the tumor	$7.5 \times 10^6\ cell/cm^3$
h_0	Scaling parameter for VEGF	$10^3\ pg/cm^3$
h_1	Threshold concentration of VEGF	$1.48 \times 10^3\ pg/cm^3$
λ_7	Delivery rate of oxygen	$6.3936 \times 10^2\ pg/cell/day$
D_w	Diffusion coefficient of oxygen	$4.32 \times 10^{-2}\ cm^2/day$
λ_8	Consumption rate by T cells	$1.61568 \times 10^{-8}\ cm^3/cell/day$
λ_9	Consumption rate by MDSC	$1.61568 \times 10^{-8}\ cm^3/cell/day$
λ_{10}	Consumption rate by T_{reg}	$1.61568 \times 10^{-8}\ cm^3/cell/day$
λ_{11}	Consumption rate by tumor cells	$1.728 \times 10^{-8}\ cm^3/cell/day$

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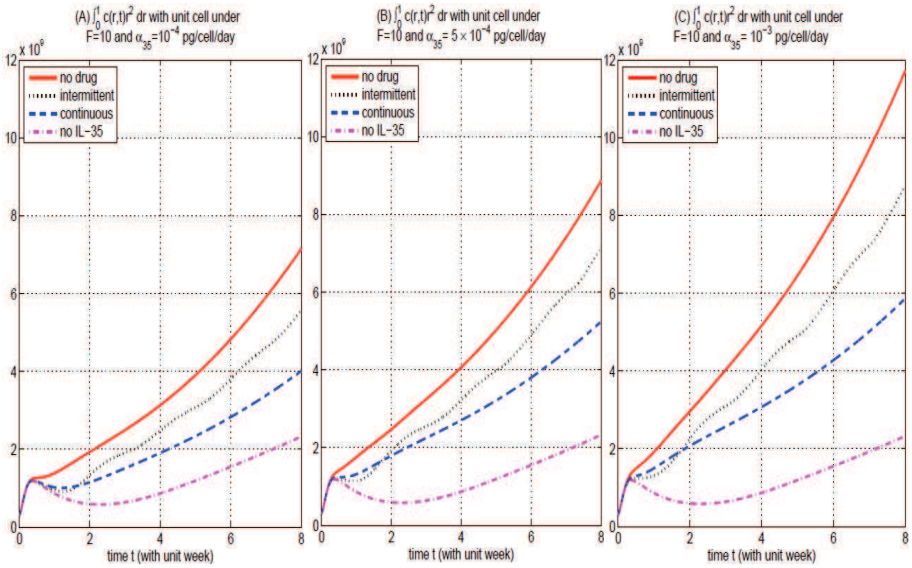

FIGURE 6. **Comparison of continuous versus intermittent treatment in different production rate α_{35} with drug strength $F = 10$.** (A), (B), and (C) are the profiles of total numbers of $c(r,t)$, under $\alpha_{35} = 10^{-4}$ $pg/cell/day$, $\alpha_{35} = 5\times10^{-4}$ $pg/cell/day$, and $\alpha_{35} = 10^{-3}$ $pg/cell/day$, respectively. The solid curve is for case of no dozing with anti-IL-35. The dashed and dotted curves are for tumor cells with continuous and intermittent drug injections, respectively. The dashed-dot curve $(-.-)$ is the case that there is no IL-35 in the tumor microenvironment, i.e., $\alpha_{35} = \beta_{35} = \gamma_{35} = 0$ and $I_{35}(r,0) \equiv 0$, for $0 \le r \le L$.

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