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Dynamic Modelling of T Cell Vaccination Response

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ABSTRACT

In our previous work, a mathematical, agent-based dynamic model was developed which simulates the response of the mammalian omentum to a T cell vaccine injection during the expansion phase. The model tracks how each individual naïve T cell interacts with antigen presenting cells, and subsequently primes and divides over an 8-day period following vaccine injection. The model works from first principles; individual phenomena based on experimental observation and theory are incorporated into the model, and the collection of many such phenomena together create a nuanced model of the system as a whole. In this work, we show that the model works well in other relevant tissues, such as the spleen.

Keywords: T cells, stochastic, dynamic, modeling, vaccine

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ORIGINAL MODEL

Background

In our previous work [1], a mathematical, stochastic, dynamic model called the STORE model (STochastic Omentum REsponse) was developed in MATLAB to simulate T cell priming and division in the omentum after vaccination. The model is stochastic and agent-based such that each individual agent is tracked over time during the dynamic simulation valid up to a period of 8 days after vaccine injection. The individual agents include antigen presenting cells and T cells at various stages during vaccination:

A = naïve T cells
B = primed T cells
C = primed T cells which have matured and divided once
D = C cells which have divided
E = D cells which have divided
F = E cells which have divided
G = F cells which have divided
H = G cells which have divided
I = H cells which have divided
J = I cells which have divided, plus all subsequent generations
P = antigen presenting cells (APCs)

The model inputs include the initial count of T cells injected, the arrival rate of APCs which is the time required for APCs to travel from the site of injection to the tissue of interest, the number of APCs or antigens that enter the tissue, the division time for J, as well as probabilities of cells leaving the system or maturing (see [1] for specifics). The model uses probability distributions for each cell type to mature, divide and leave the system, based on their age and/or concentration within the tissue. At each time step, random number generators are used in conjunction with probability distribution functions to determine the action (or inaction) of each agent in the system.

The previous work showed that the model fit experimental data well in mice for multiple experimental data sets provided by different groups. The model was shown to have sufficient complexity to explain how multiple different behavioural regimes (such as cyclic behaviour vs. pulse behaviour) naturally arise from the system given different input stimuli. However, the model was previously developed only for the omentum and only verified with data for the omentum. In this work, we investigate whether the model is also predictive for other relevant tissues, such as the lymph nodes, spleen, and peritoneum. Most of the underlying phenomena in the omentum also occurs in these other tissues, and so the model that was developed for the omentum should have some predictive qualities as well in these other tissues.

APPLICATION TO OTHER TISSUES

The mathematical model initially developed for the omentum could be extended to other tissues including the peritoneum, draining lymph nodes, non-draining lymph nodes, and the spleen. However, experimental data shows that there are timing differences in when the explosive growth rates of T cells actually occur.

T Cell Counts in Other Tissues

Applying the MATLAB model for the omentum to other tissues in the body would be significant as the route of T cell migration in the body can be determined. Understanding T cell behaviour and their migration patterns between different tissues help explain important phenomena such as central

memory and resident memory (different aspects of protective immunity) as well as the stochastic nature behind immunization. Recent experiments at the University of Pennsylvania [2] examined the cell count of T cell stages after injecting T cells intravenously (IV) 24 hours before vaccinating intraperitoneally (IP), which is through the peritoneum (in the abdomen). Five different tissues were examined: draining lymph nodes, non-draining lymph nodes, omentum, peritoneum and spleen. The study was done 15 mice which were tracked for 90 hours with data collected from at a time points 42, 66 and 90 hours post injection (5 mice per time point). We note that these data are in preparation for publication and so only summaries and averages are provided in this work.

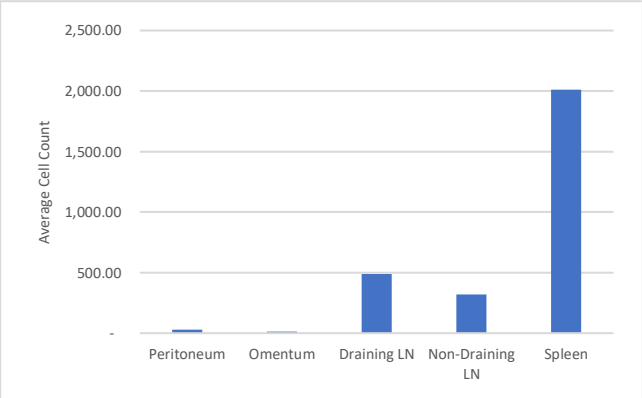

Figure 1. Average total cell count of T cells after 42 hours.

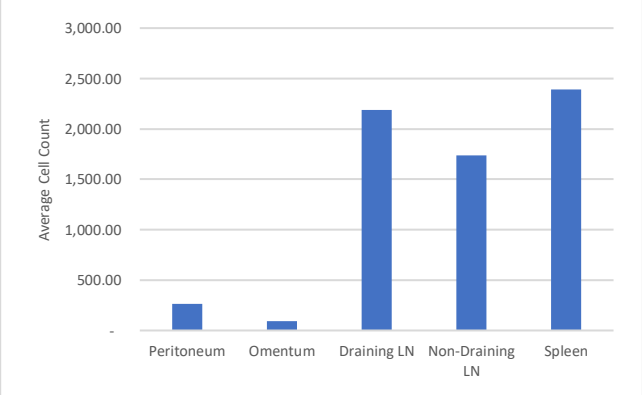

Figure 2. Average total cell count of T cells after 66 hours.

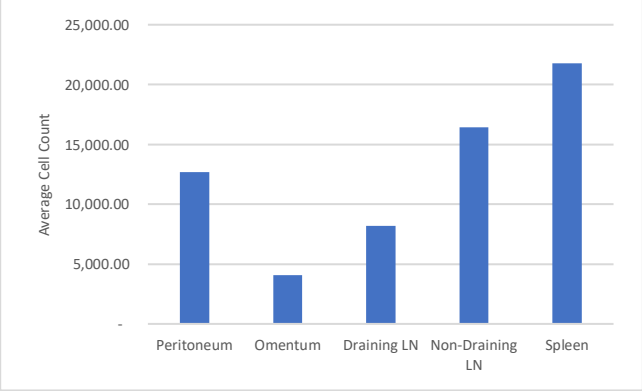

Figure 3. Average total cell count of T cells after 90 hours.

The average cell counts of each group of five mice are shown in Figure 1. The majority of the T cells accumulate in the spleen, with some in the draining and non-draining lymph nodes and a small number of cells in the omentum and peritoneum. Figure 2 shows the later time point where the lymph nodes become more active than the spleen as cells are dividing more rapidly. The results in Figure 3 shows omentum and peritoneum are the last tissues for T cells to accumulate.

Method of Injection Influences Cell Counts

The distribution of T cells is based on the method of injection. When cells are injected IV, cells travel through the circulatory system and majority of the cells end up in the spleen as there is a large supply of blood. Lymph nodes have a small blood supply, however due to the large number of lymph nodes in the body, an adequate amount of T cells can also be found in the lymph nodes. Alternatively, when the vaccine is injected IP and APCs are generated in the peritoneum, the cells enter the lymphatic system which connects directly to the lymph nodes and no cells will enter the spleen as it is not connected to the lymphatic system. This explains why the lymph nodes become more active than the spleen even though it has more T cells. Although the majority of the T cells are in the spleen and some in the lymph nodes, all the APCs generated by IP immunization will travel to the lymph nodes and not the spleen. The APCs meet the T cells in the lymph nodes and prime them causing a chain reaction of cell divisions. On the other hand, as no APCs enter the spleen, the naive T cells present in the spleen will not be primed and therefore the cells will not divide. This explains the activeness of lymph nodes compared to the spleen. After clonal expansion of primed T cells, they leave through the lymph and blood. Some will enter the spleen through the blood supply, and some are recruited to the infection site, which are the omentum and peritoneum. This is supported by figures 1-3 which show omentum and peritoneum are the last to have accumulation of T cells due to recruitment.

SIMULATIONS OF THE SPLEEN

Because the previous analysis shows that the cell counts do not all peak at the same time in each tissue, and because of the complex interactivity between tissues, the original model developed for the omentum cannot be used directly to model the system as a whole. However, it can be readily adapted to each individual tissue by changing some key parameters and then creating additional model elements that represent the transportation of cells between tissues. As a first step, we examine the adaptation of the omentum model for the spleen.

T Cell Activity in the Spleen

The same mathematical model was applied to an unpublished dataset from University of Colorado [3] (again, only averages are presented), where they tracked the activity of T cells in the spleen of 19 mice. T cells were injected IV 12 hours prior to injecting the APCs IV. Two sets of mice were used in this study: wild type (WT) and knockout (KO). WT mice are found in natural populations and KO mice are genetically modified by removing a gene to study its effects. Data were collected from 3 mice at a time after approximately 24, 36, 48, 72, 96 and 168 hours with an exception of using 4 mice for data collection at 72 hours.

The MATLAB model originally developed for the omentum and for a different set of experiments was modified for the spleen simply by changing the values of some model parameters (such as the reproduction rate of J) to best fit the experimental data. The fundamental theory and underlying phenomena was not modified. The simulation results for the WT mice are shown in Figures 4-9, where the lines are the simulation, and the circles are the experimental average cell counts of the indicated cell type at the appropriate time point. We note that some cell type counts in this experiment are extremely small, and that data points are not integers because they are averages of 3-4 data points. The model itself is restricted to only having integer values.

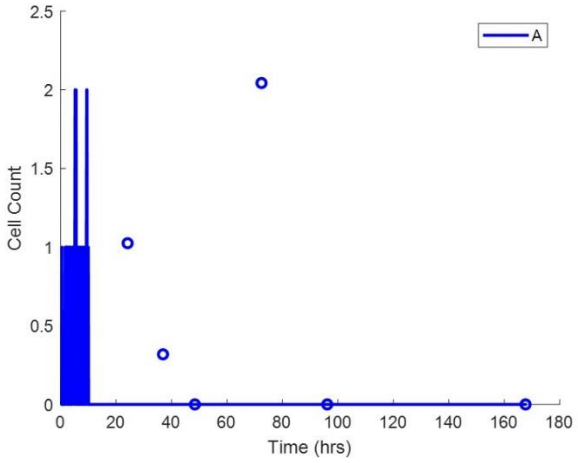

Figure 4. Simulation results for A cells (naïve T cells) in WT mice.

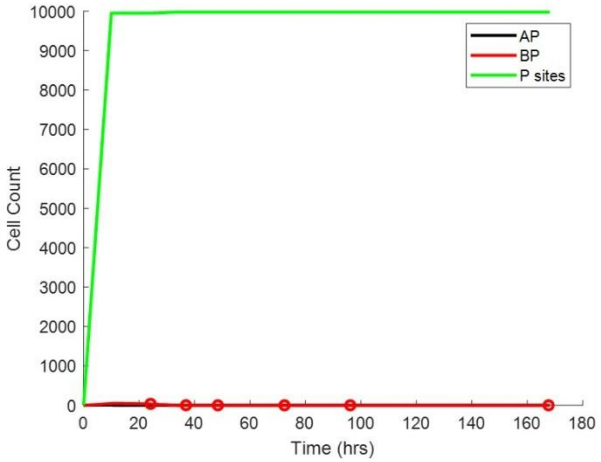

Figure 5. Simulation results for AP (naïve T cells bound to APC), BP (matured AP) and P sites (total APC binding sites) in WT mice.

The arrival rate of APCs in the simulation was set such that it takes 10 hours for all APCs to arrive in the spleen (starting at time zero and continuing at a constant rate until 10 hours have elapsed) to simulate the effects of IV injection. This is more rapidly than if it were to be injected IP and travel through the lymphatic system (requiring about 24 hours to arrive). The division time parameter for J was also set to 8 hours as T cell replication was occurring at a faster rate in the spleen (in the previous omentum model, 24 hours used [1]). This can be seen in Figure 8. The leaving probabilities of BP (p_{BP}), E through H (p_{EH}) and I through J (p_{IJ}), see [1] for definitions, were also decreased (from the omentum model) down to 0.001, 0.001 and 0, respectively.

From the results, the cells in the spleen seem to accumulate faster than in the omentum. It can be seen in Figure 4 that the number of naive T cells (A) present in the spleen were only 1 or 2 cells which is extremely small compared to the data from University of Pennsylvania. This is because APCs were injected in at least 200 times the magnitude of T cells, therefore APCs were in a large excess and consumed majority of the naive T cells at a rapid rate. Hence, the initial number of T cells (N_{A0}) was set as 50 and the initial number of APCs (N_{P0}) were set at a ratio of $N_{A0}/0.005$.

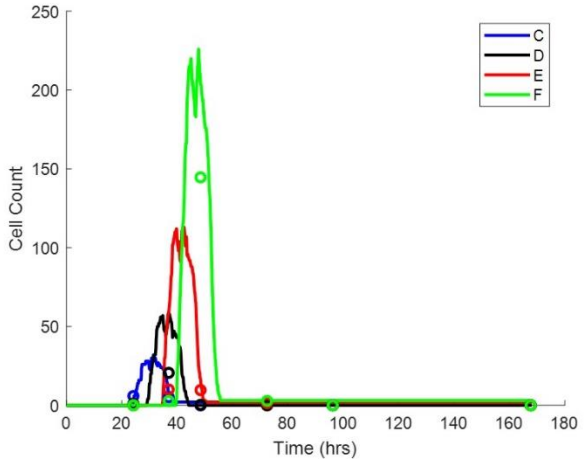

Figure 6. Simulation results for stages C through F in WT mice.

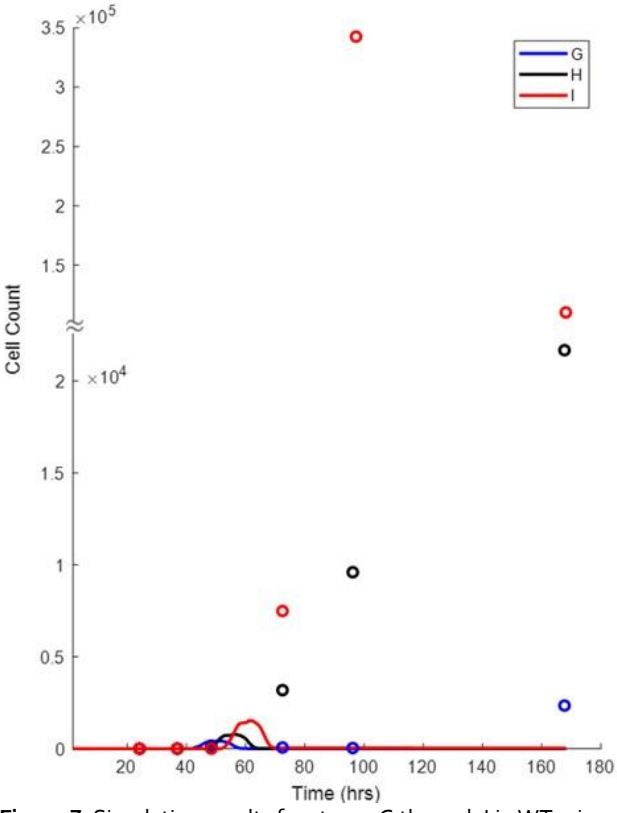

Figure 7. Simulation results for stages G through I in WT mice.

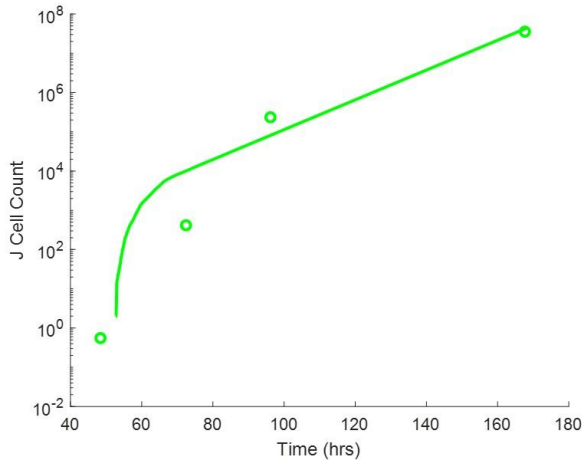

Figure 8. Simulation results for J cells in WT mice.

This simulation results from using these parameters can be seen in Figure 5 as the green curve represents total APC sites which is in excess. Having APC in excess results in "pulse-like" behaviour, which is in contrast to having excess naïve T cells which results in "cycle-like" behaviour [1]. In these experiments, having excess APC counts mean that naïve T cells are almost immediately paired with APCs upon arrival in the spleen, which is why cell counts of type A and BP are so low as shown in Figures 4 and 5. The model reflects this in the experiment quite well.

As the cells start to divide (Figure 6) the pulse behaviour is evident in cell divisions C through F, with each stage going through a single maximum before they have all either divided or have left the system. The simulation fits the data extremely well considering the model was created and validated using a different injection method, tissue, and application with drastically different number of T cells and APCs. This demonstrates that the underlying physical phenomena considered in the model characterises the cell interactions within a tissue well.

However, Figure 7 shows the simulation fits the data poorly for cells G through I. The peaks from the simulation are not occurring at the same time as the data and the data points are orders of magnitude too high for the simulation peaks to possibly reach. The data also do not follow the theorem used by the model, which is considers that almost all cells double by division after 5.3 hours and a small amount would remain in the system. By using this principle, the subsequent divisions should peak at approximately double the peak cell count of the previous stage (i.e. the peak of G should be double of the peak of F). However, the data points for G through J are significantly higher than the previous stages.

Possible explanations for these results are either the cells are dividing at an extremely rapid rate due to an unknown phenomenon, more likely, or the experimental method used to differentiate the cells into stages is not accurate. This could happen as cell count in stages G through J are much higher than the previous stages which can result in clustering of cells. This can cause the gating of cells obtained from flow cytometry to be inaccurate and group the cells into the incorrect stages. As a result, the number of cells in each stage are likely to be a combination of G, H, I and J cells, which would explain the extremely high magnitude in cell count.

Figure 8 shows a semi-log plots of type J counts, noting that type J cells include all subsequent generations of J and their divisions. Because of this grouping, type J grows exponentially, doubling about every 8 hours. Since the simulations predict both the value and timing of the peak extremely well with experimental data, it is likely that the unexpectedly high and irregular experimental data for types G- I are due to measurement error.

Effects of Gene Removal

KO mice were genetically engineered as the IL-27R gene was removed from each mouse. Data were collected in the same fashion [3] and the spleen model was applied. The simulation results for KO mice are shown in Figure 9-13.

The model used the same parameters from the WT mice except for the division time of J which was slower in KO mice. This is expected, since inhibiting IL-27 signaling is likely to reduce cell division rates, cause J cells to leave the system at a greater rate, and/or cause J cells to die at a greater rate [4]. The replication time was changed from 8 to 10 hours and the simulation results of J cells are shown in Figures 13. The results in Figures 9-12 show the KO mice data set is similar to WT data for stages A through I, and the simulation fits the data very well. Since all other parameters were unchanged from the first experiment, this serves to validate the spleen model.

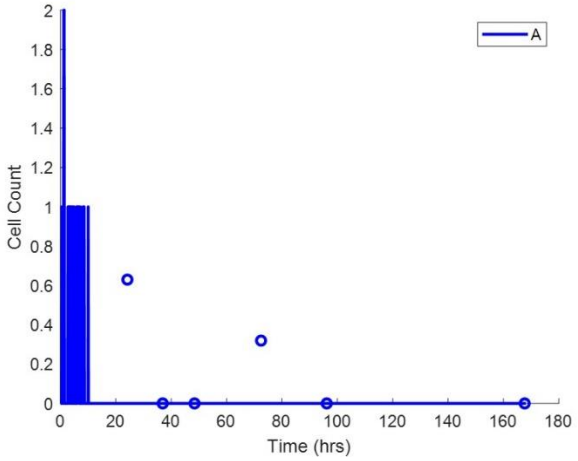

Figure 9. Simulation results for A cells (naïve T cells) in KO mice.

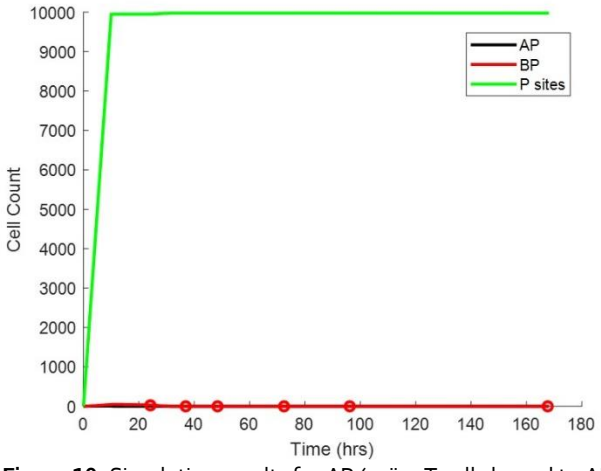

Figure 10. Simulation results for AP (naïve T cells bound to APC), BP (matured AP) and P sites (total APC binding sites) in KO mice.

CONCLUSIONS

The STORE model, which was originally developed for the omentum, can also accurately predict T cell responses in the spleen by changing four model parameters relating to the probabilities that certain cell types leave the system or die at any given time, as well as the rate at which type J cells divide. This shows that T cell priming and division is likely governed by the same fundamental phenomena in both tissues, but with some differences that require further study and explanation. These differences may be unique to the tissue, or, they may be the result of other cross-tissue phenomena, such as how T cells are transported throughout the system between tissues. It can also be concluded that genetic deletion of IL-27R from T cells likely either results in slower replication of type J cells, and/or, an increase in the leaving rate of J from the system, since all other model parameters remained the same when comparing WT and KO mice.

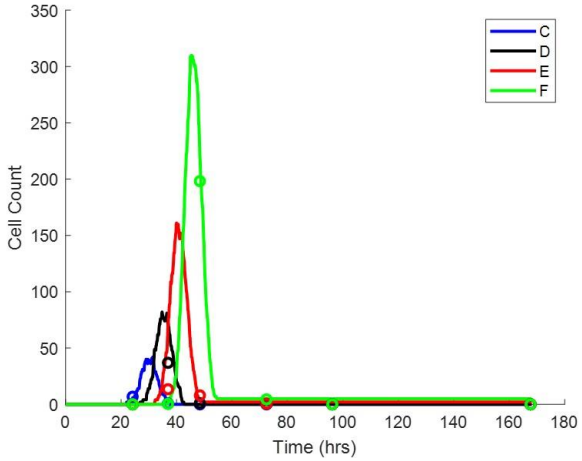

Figure 11. Simulation results for stages C through F in KO mice.

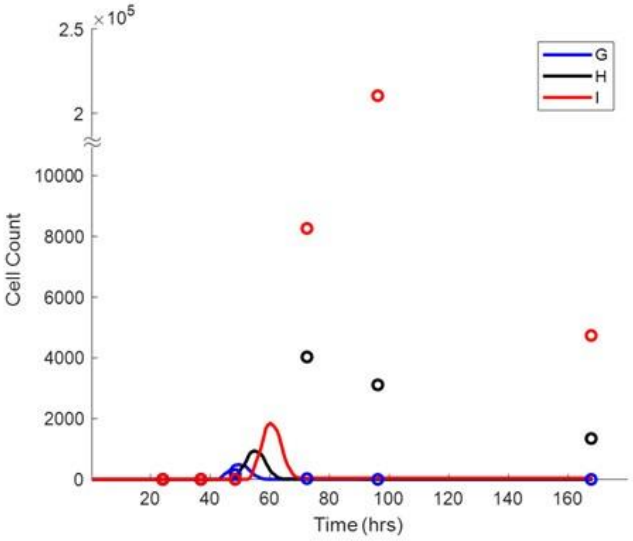

Figure 12. Simulation results for stages G through I in KO mice.

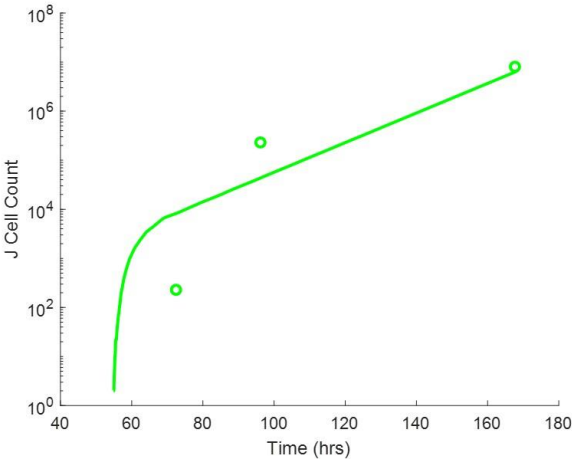

Figure 13. Simulation results in a semi-log plot for J cells in KO mice.

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