Understanding the Connection between Nanoparticle Uptake and Cancer Treatment Efficacy using Mathematical Modeling

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Nanoparticles have shown great promise in improving cancer treatment efficacy while reducing toxicity and treatment side effects. Predicting the treatment outcome for nanoparticle systems by measuring nanoparticle biodistribution has been challenging due to the commonly unmatched, heterogeneous distribution of nanoparticles relative to free drug distribution. We here present a proof-of-concept study that uses mathematical modeling together with experimentation to address this challenge. Individual mice with 4T1 breast cancer were treated with either nanoparticle-delivered or free doxorubicin, with results demonstrating improved cancer kill efficacy of doxorubicin loaded nanoparticles in comparison to free doxorubicin. We then developed a mathematical theory to render model predictions from measured nanoparticle biodistribution, as determined using graphite furnace atomic absorption. Model analysis finds that treatment efficacy increased exponentially with increased nanoparticle accumulation within the tumor, emphasizing the significance of developing new ways to optimize the delivery efficiency of nanoparticles to the tumor microenvironment.

Cancer represents the 2nd major cause of death in the United States, and one out of eight women is estimated to develop invasive breast cancer in her lifetime1. Breast cancer tumors are heterogeneous, and the series of events which cause them to grow, shrink, or metastasize are complex, involving interactions with and influences from their microenvironment1. It is known that the heterogeneity of the breast cancer tumor greatly complicates our understanding of the disease and the development of effective treatment1. In fact, most tumors are heterogeneous both phenotypically and functionally1, resulting in variable traits among different tumors. Understanding an individual’s response based on these differing traits is essential for predicting and improving patient-specific treatment response.

Due to drug toxicity and non-specificity, a spectrum of different particles have been developed for both particle-based drug delivery and for imaging of particle distribution, including superparamagnetic iron oxide nanoparticles4, lipid bilayer encapsulated nanoporous silicon or mesoporous silica particles for drug/cargo delivery5–7, and silica based nanoparticles8, to name a few. Here, we discuss the use of mesoporous silica nanoparticles (MSNPs), which possess the benefits of a high cargo capacity, due to their immense internal surface area

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imaging, using methods such as transmission electron microscopy or optical microscopy, or by elemental analysis of nanoparticles biodistribution is done through organ dissection after injection of labeled nanoparticles, followed by using appropriate contrast agents. However, successful prediction of treatment outcome based solely on theory based on this model in order to predict nanoparticle-based treatment efficacy using quantitative experimental data obtained from measured nanoparticle biodistribution.

Measurement of drug distribution in vivo is often difficult and expensive. Typically, quantitative analysis of nanoparticle biodistribution is done through organ dissection after injection of labeled nanoparticles, followed by imaging, using methods such as transmission electron microscopy or optical microscopy, or by elemental analysis using inductively coupled plasma-atomic emission. Nanoparticle distribution can also be measured in vivo using magnetic resonance imaging and magnetic particle imaging. Here, capitalizing on the low natural abundance of elemental silicon in mammals, we performed Si elemental analysis of the major organs in order to measure MSNP concentrations, and then compared these quantified MSNP accumulation values to changes in tumor volume. By using our theory to link measured tumor growth with nanoparticle distribution and concentration, and considering the effects of vasculature and diffusion characteristics, we were able to successfully predict the in vivo therapeutic efficacy of MSNP-delivered doxorubicin to 4T1 breast cancer tumors in mice.

Results and Discussion

Cancer stage at the time of diagnosis is demonstrated to be an important predictor of morbidity and survival. Five-year survival rates for breast cancer are 99% when diagnosed pre-metastasis, but with a significant reduction to only 25% five-year survival rate when the tumor has metastatized. In order to better understand the difficulties of effective therapeutic treatment when patients are diagnosed at a later stage, our experiments focused on treating tumors that were relatively large with distant metastases prior to the start of a treatment. Accordingly, we implemented a 4T1 cell line experiment in BALB/c mice, in order to study stage IV human breast cancer with metastasis in the presence of an active immune system.

Treatment efficacy between MSNPs loaded with doxorubicin (Dox) and free Dox was compared at the same dosage; phosphate buffered saline (PBS) was used as a control in a third treatment group. Tumor size measurements in mm$^3$ are shown in Fig. 1 for three groups of seven mice each treated using PBS (control), free Dox, or MSNPs loaded with Dox. Due to this treatment being administered at a later stage of breast cancer, it can be observed that free Dox treatment is not effective at a late stage; but the nanoparticle treatment shows some efficacy (see Supplementary Fig. S1 for each individual measurement). However, we note that statistically significant differences in tumor response between different treatment groups was not identified. This warrants additional...
experiments on a larger scale with more data points to demonstrate the treatment efficacy for this particular nanoparticle.

*In vivo* biodistribution of nanoparticles based on size, shape, composition, and surface characteristics is still not well understood, as are the details of nanoparticle removal from circulation by the reticuloendothelial system. To gain a better understanding of these important parameters, we used graphite furnace atomic absorption (GFAA) to measure silicon (Si) concentration and distribution within tissues of interest. The Si concentration in the control (PBS) group was used as a baseline for the background Si concentration which occurs naturally in tissues (Si has important biofunctionality, and thus is found in trace quantities in many tissues). As expected, we observed that the amount of naturally occurring Si in the control tissues was low relative to the signal of MSNP in treated tissues. Figure 2 shows measured values of elemental Si determined by GFAA, presented as the mass percentage of Si in the corresponding tissue being tested in mouse organs from the control and Dox loaded MSNP treatment groups after 9 days of treatment and sacrifice. The tissues tested were tumor, kidney, liver, spleen, as well as a measured sum of all organs. The sum of all organs tested corresponded to ~2–4.4% of the total injected Si dose, as shown in Supplementary Fig. S2.

Mice, even within the same treatment group, demonstrated a wide range of *f*<sub> kill</sub> responses, indicated by the large standard deviation seen in tumor volumes in Fig. 1 (error bars). Moreover, the concentrations of Si deposited in the liver, spleen, kidney, and tumor were shown to vary without correlation between uptake in the tissues measured in our study. Figure 2 shows measured values of elemental Si determined by GFAA, presented as the mass percentage of Si in the corresponding tissue being tested in mouse organs from the control and Dox loaded MSNP treatment groups after 9 days of treatment and sacrifice. The tissues tested were tumor, kidney, liver, spleen, as well as a measured sum of all organs. The sum of all organs tested corresponded to ~2–4.4% of the total injected Si dose, as shown in Supplementary Fig. S2.

Figure 2. MSNP deposition (Si mass %) in liver, spleen, kidneys, tumor, sum of organs, and average Si concentration naturally in tissues (control group) taken post-sacrifice (day 9). Data were obtained using GFAA spectrophotometry. Error bars are calculated based on the standard additions method used to calculate standard deviation of Si concentrations.

Figure 3. Tumor delivery efficiency (%ID). Data were obtained using GFAA spectroscopy. Naturally occurring Si (measured by testing control tumors in mice not exposed to MSNPs) was subtracted from absolute Si mass % in tumor. Standard deviation is shown in error bars (n = 7 for control and MSNP groups). Delivery efficiency calculation is described in Methods in section “Graphite Furnace Atomic Absorption Spectrophotometry.”
measurable response to treatment until day 7, resulting in only two data points; therefore, that most model values are statistically significant at 95% confidence except for MSNP 5. MSNP 4 and 7 did not show quadratic curves described in Eq. 4.

Deposition values are also shown in Fig. 2 (MSNP deposition) and in Fig. 4 ($R^2$, $\theta$, $t_0$), showing the exponential relation to the tumor $f_{\text{kill}}$ coefficient calculated using Eq. 4. $p$-values and $R^2$ are calculated with respect to quadratic curves described in Eq. 4.

Table 1. Tumor $f_{\text{kill}}$ coefficients ($\theta$), as described by Eq. 4, show a similar order to Si deposition values. The Si deposition values are also shown in Fig. 2 (MSN deposition) and in Fig. 4 ($R^2$, $\theta$, $t_0$), showing the exponential relation to the tumor $f_{\text{kill}}$ coefficient calculated using Eq. 4. $p$-values and $R^2$ are calculated with respect to quadratic curves described in Eq. 4.

| Mouse  | Si % in tumor | $t_0$ (time tumor begins to respond to treatment in days) | $\theta$ (quadratic response coefficient) | $p$-value | $R^2$ (quadratic) |
|--------|---------------|----------------------------------------------------------|------------------------------------------|-----------|------------------|
| MSNP 4 | 0.00513       | —                                                        | 0.4621                                   | —         | —                |
| MSNP 7 | 0.00535       | —                                                        | 0.3068                                   | —         | —                |
| MSNP 2 | 0.00372       | 0                                                        | 0.0096                                   | 0.0030    | 0.9648           |
| MSNP 5 | 0.00362       | 0                                                        | 0.0067                                   | 0.0050    | 0.9499           |
| MSNP 1 | 0.00360       | 0                                                        | 0.0064                                   | 0.0110    | 0.9155           |
| MSNP 5 | 0.00138       | 0                                                        | 0.0027                                   | 0.1990    | 0.4728           |
| MSNP 6 | 0.00260       | 0                                                        | 0.0013                                   | 0.0060    | 0.9409           |

Figure 4. Si concentration and $f_{\text{kill}}$ coefficient ($\theta$) determination. $\theta$, explained in Eq. 4, is predicted based on Si absolute mass percentage in tumor, as measured using graphite furnace atomic absorption (GFAA). $R^2 = 0.817$, $p_{0.05} = 0.0007$ for quadratic $f_{\text{kill}}$ Coefficients calculated after 9 days of treatment and sacrifice. This was determined by the best fit between $f_{\text{kill}}$ and Si concentration using an exponential fit (which represents the best fitting function among many we have tested, including linear and nonlinear functions, e.g., quadratic, sigmoidal, the Michaelis-Menton, and the Hill function). Experimental mouse tumor $f_{\text{kill}}$ was determined using Eq. 2 for mice treated with MSNPs. Model mouse tumor $f_{\text{kill}}$ was determined by optimizing values for $t_0$ (days in integer values), described in Eq. 4. Standard deviation for measured Si % in each mouse’s tumor treated with MSNPs is shown for experimental values on the x-axis.

reaching cancer cells and their subcellular compartments in vivo is much less than 0.7%ID because nanoparticles need to cross the tumour extracellular matrix to reach the cancer cells28. Hence, our data seems well consistent with Welhelm et al’s paper. One paper used elemental analysis, ICP-AES, to measure silica nanoparticle concentration, of which the %ID was determined to be 0.29, 1.6, and 10.8%ID35, most of the quantifications used to calculate the average of 0.7%ID in a tumor used PET scans as a method of quantification16,21,30,31. Thus, the biodistribution of nanoparticles was observed to show significant variability, even amongst similar mice under the same treatment protocol. Blood volume fraction (i.e., the volume of the tumor occupied by blood vessels) was previously shown to be an important factor in predicting $f_{\text{kill}}$ in human colorectal cancer metastasized to the liver35.

Many current nanoparticles have achieved the capability to release drugs at a nearly constant, sustained rate for a period of days, weeks, or even months36–39, although this rate may be dependent on other physicochemical properties of the particles, such as the surface chemistry and pore size36. In vivo, this nearly constant drug release rate results in an approximately unchanged rate of change of drug flux (denoted by $F$) across blood vessels. By further assuming a linear drug uptake by cancer cells, we have developed a special form of $f_{\text{kill}}$ for predicting treatment efficacy for nanoparticle-based drug delivery systems37. We found that tumor response in vivo to Dox loaded nanoparticles occurs quadratically over time, at least for the first several days ($f_{\text{kill}} = \theta t_0 - t^2$, i.e., Eq. 4, where $\theta$ is the tumor $f_{\text{kill}}$ coefficient; also see Methods), and have further validated this model using experiments on a breast cancer mouse model. Accordingly, we used this quadratic tumor response model to link the MSNP deposition with measured changes in tumor volume (relative to control). The quadratic tumor response coefficient (i.e., $f_{\text{kill}}$ coefficient; $\theta$) was determined to have an exponential relationship with MSNP deposition in the tumor tissue (Fig. 4); note that we simply applied a phenomenological approach to identification of the relationship between $\theta$ and Si deposition. $\theta$ was found to be predictable based on tumor silicon content with 95% confidence ($R^2 = 0.817$, $p_{0.05} = 0.0007$) based on the quadratic curve for $f_{\text{kill}}$ described in Eq. 4. This indicates that increasing chemotherapy drug delivery, using a MSNP transport vector, results in an exponentially greater rate of tumor kill. Values for comparison are shown in Table 1, along with statistics that indicate that most model values are statistically significant at 95% confidence except for MSNP 5. MSNP 4 and 7 did not show measurable response to treatment until day 7, resulting in only two data points; therefore, $p$-values for $\theta$ could not be determined due to an insufficient number of points. As such, these two mice were removed from further analysis. Together, this indicates that MSNP uptake is an important factor in determining tumor treatment efficacy. However, more tumor measurements and/or a longer experiment would be beneficial to validate statistical significance with the model predictions.
We then performed correlation analysis to compare model results (computed as \( f_{\text{kill}} = 0.000172 \cdot e^{1.664.39 \cdot \text{Si} \cdot t^2} \), where Si is tumor Si mass %) and the corresponding time course MSNP experimental data as shown in Fig. 1; also see Fig. S3. We obtained correlation coefficient \( r = 0.89 \) and \( p < 0.001 \), and thus consider the model to be acceptable in predicting MSNP-based treatment outcome with absolute Si mass percent as input.

Cancer treatment may be improved by using MSNPs as chemotherapy delivery vessels, which allow for an increased effective drug dose to be delivered to the tumor site due to drug sequestration within the particles during transit to the site, resulting in reduced uptake by the reticuloendothelial system and longer circulation time. We have provided further insight into this drug delivery system using MSNPs in a murine 4T1 in vivo tumor model combined with a mathematical modeling description of drug efficacy. In particular, our mathematical model demonstrates that an increase in MSNPs delivered to the tumor exponentially increases the cell kill at early times in the treatment, leading to improvements in overall treatment outcome. The major hurdle is thus increasing tumor MSNP delivery over current methods, as any increase in delivery to the tumor is expected to significantly improve treatment efficiency. In this perspective, active tumor targeted delivery of chemotherapy via targeting ligand modified nanoparticles is expected to enhance treatment efficacy. We also clarify that, as described in our prior work, the drug concentration used to derive the \( f_{\text{kill}} \) model is the concentration at the blood vessel wall, which is assumed to be a constant and is averaged over the duration of treatment, i.e., the actual drug concentration in the tissue which reaches the tumor was not measured previously. In the present work, we have obtained an actual measurement for the estimated drug concentration in the tissue through measuring the carrier (MSNPs) loaded with Dox in the tumor and MSNP uptake in organs.

Moreover, if the quadratic \( f_{\text{kill}} \) coefficient could be determined early on, the treatment efficacy could be predicted by our mathematical model. It has been demonstrated that tumor exponential growth rate constants were correlated to patient survival. Here, we demonstrate that, due to external stresses and regression in tumor size due to treatment, the quadratic coefficient following treatment is predictive of treatment\(006Et \) uptake and therefore \( f_{\text{kill}} \) model. We have provided further insight into this drug delivery system using MSNPs in a murine 4T1 tumor model combined with a mathematical modeling description of drug efficacy. In particular, our mathematical model demonstrates that an increase in MSNPs delivered to the tumor exponentially increases the cell kill at early times in the treatment, leading to improvements in overall treatment outcome. The major hurdle is thus increasing tumor MSNP delivery over current methods, as any increase in delivery to the tumor is expected to significantly improve treatment efficiency. In this perspective, active tumor targeted delivery of chemotherapy via targeting ligand modified nanoparticles is expected to enhance treatment efficacy. We also clarify that, as described in our prior work, the drug concentration used to derive the \( f_{\text{kill}} \) model is the concentration at the blood vessel wall, which is assumed to be a constant and is averaged over the duration of treatment, i.e., the actual drug concentration in the tissue which reaches the tumor was not measured previously. In the present work, we have obtained an actual measurement for the estimated drug concentration in the tissue through measuring the carrier (MSNPs) loaded with Dox in the tumor and MSNP uptake in organs.

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**Materials and Methods**

**Mathematical modeling.** We recently developed a series of mathematical models in closed form for predicting tumor response to treatment based on time- and space-dependent drug diffusion and perfusion properties. A generalized model presented in can provide predictions of outcome for both conventional chemotherapy with a specific dosing and timing regimen and nanoparticle-based treatment. \( f_{\text{kill}} \) (i.e., the fraction of tumor killed by treatment) is defined as:

\[
f_{\text{kill}} = 1 - \frac{V(t)}{V_C(t)}, \quad (1)
\]

where \( V \) is tumor volume at time \( t \), \( i \) indicates drug treatment group (Dox or Dox loaded MSNPs), and \( C \) indicates the control group. Normalizing tumor volume at a given time \( t \) to initial volume, we have

\[
f_{\text{kill}} = 1 - \frac{V(t)/V(t_0)}{V_C(t)/V_C(t_0)}, \quad (2)
\]

where \( t_0 \) is determined to be the initial day when treatment was started; in our analysis here, \( i \) simply indicates either free DOX or MSNP treatment group.

Assuming that drug-loaded nanoparticles can accumulate within tumors and continuously release drugs at a nearly constant rate over a certain time interval (especially at the initial phase of a treatment), we derived a special form of \( f_{\text{kill}} \):

\[
f_{\text{kill}} = \frac{F \cdot \lambda_k t^2}{2V_{t,0}}, \quad (3)
\]

where \( F \) is the flux of drug across blood vessel walls, \( \lambda_k \) is the death rate of tumor cells, \( V_{t,0} \) is the tumor volume when tumor begins to respond to treatment (positive \( f_{\text{kill}} \)), and \( t \) is time. Note that there is another key assumption we made to the original \( f_{\text{kill}} \) model, which is composed of a system of differential equations, in order to develop this simplified form: a drug administered as bolus at a certain dose level has the same effect as the same total amount of drug administered over several months at a constant, smaller dose level. That is, this model functions for a number of situations, including (1) single drug injection at the beginning, (2) multiple drug injections over the course of treatment, and (3) continuous drug administration. Regardless of how we administer the drug, the treatment system can be modeled as a continuous drug delivery system. This assumption has been validated previously in vivo and in patients across different types of cancer.

Parameters for best model fits to experimental data (determined by Eq. 2) with the model's predictions from Eq. 3 are derived from:
where coefficients $A$ and $B$ are fit to determine best values for prediction between Si absolute mass percentage and the model output, $\theta_0$. $A$ and $B$ are tumor and drug specific coefficients specific to 4T1 breast cancer given treatment when tumors are ~500 mm$^3$ when beginning treatment. $A$ and $B$ are the same for all 5 mice given the treatment described under the experimental description used to describe the relationship between Si mass % deposited in 4T1 breast tumors and $\theta_0$ shown in Fig. 4.

**Experiment description.** **Accordance statement.** Mouse experiments were performed using protocol approved by the UNM Office of Animal Care Compliance. All methods were carried out in accordance with relevant guidelines and regulations. Six- to eight-week-old female BALB/c female mice were given subcutaneous injections of $5 \times 10^5$ 4T1 (ATCC® CRL2539™) cells into the right flank. Tumors were grown for two weeks before treatment initiation. Average tumor volumes, calculated from diameters measured externally with calipers, are shown in Fig. 1. Mice were randomly divided into three treatment groups (7 mice/group, 21 mice total): control (PBS), free doxorubicin 1 mg/kg per treatment, 1 mg acetylated MSNPs (50 nm, 2.5 nm pores) loaded with doxorubicin, equivalent 1 mg/kg doxorubicin per treatment). Acetylated MSNPs were made using the protocol described in Townson et al. [12], and loaded with doxorubicin using the drug loading protocol for water soluble doxorubicin in Lin et al. [16]. Treatment was given starting 2 weeks after tumor cell injections. Treatment days were as follows ($t = 0$ is 2 weeks following tumor injections): 0, 2, 4, and 7. All mice were sacrificed on day 9. Tumor measurements were taken on days: 0, 3, 7, 8, and 9. Tissues were excised and fixed in 4% formaldehyde diluted in PBS, and then Si contents were determined using graphite furnace atomic absorption spectrometry as described below. Statistical analysis was conducted using Matlab, Excel, and Graphpad Prism.

**Graphite Furnace Atomic Absorption Spectrophotometry (GFAA).** Analysis of Si concentration in MSNP (mesoporous silica nanoparticle) and control (PBS) treated mice tissue was tested using a THGA graphite furnace on a PinAAcle 900T Atomic Absorption Spectrophotometer (Perkin Elmer, USA). Tissues tested were tumor, kidney, spleen, and liver digested using aqueous tetramethylammonium hydroxide. Absolute mass percentages of silicon in the specific tissue were measured using the standard additions method, commonly used for samples prepared within a matrix that has a strong influence on the analyte signal (the matrix is defined as anything present in the solution that is not the analyte). In the standard additions method, tissues are spiked with differing, known concentrations of Si in order to determine the Si mass % in the tissue measured by extrapolation of the obtained curve of Si signal versus addition to zero addition; a unique signal vs. addition curve is generated for each tissue sample. Tumor (or organ) delivery efficiency, %ID, was determined by using BALB/c standard organ values from Tsai et al. [49] to estimate total organ Si mass deposited. Total Si delivered was calculated based on Si percentage (39.36% of nanoparticle mass) added during synthesis using the protocol in Townson et al. [12]. Tumor delivery efficiency, %ID, was determined using Si absolute mass percentage in the average control mice each respective organ subtracted from that of the MSNP treated mouse and dividing it by the total administered dose over the treatment duration. The delivery efficiency was measured based on the mass of Si measured in each respective organs divided by the total injected mass of Si (in the form of MSNPs). See Supplementary Information for more details on GFAA methods.

**Data availability.** All data generated or analyzed during this study are included in this published article and its Supplementary Information files.

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T.A.B., C.J.B. and Z.W. conceived and designed the research. T.A.B., E.N.C., P.N.D., Y.-S.L., J.T., E.F.W. and C.J.B. generated and analyzed the experimental data. T.A.B., V.C. and Z.W. performed model analysis. T.A.B., C.J.B. and Z.W. wrote the manuscript, with input from all authors. All authors reviewed and approved the manuscript.

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