**SUPPLEMENTARY MATERIAL FOR:**

# Pharmacokinetic/pharmacodynamics modeling of drug-loaded PLGA nanoparticles targeting heterogeneously vascularized tumor tissue

Hunter A. Miller[a] and Hermann B. Frieboes[a,b,c,d*]

[a]Department of Pharmacology and Toxicology, University of Louisville, Louisville, KY, USA

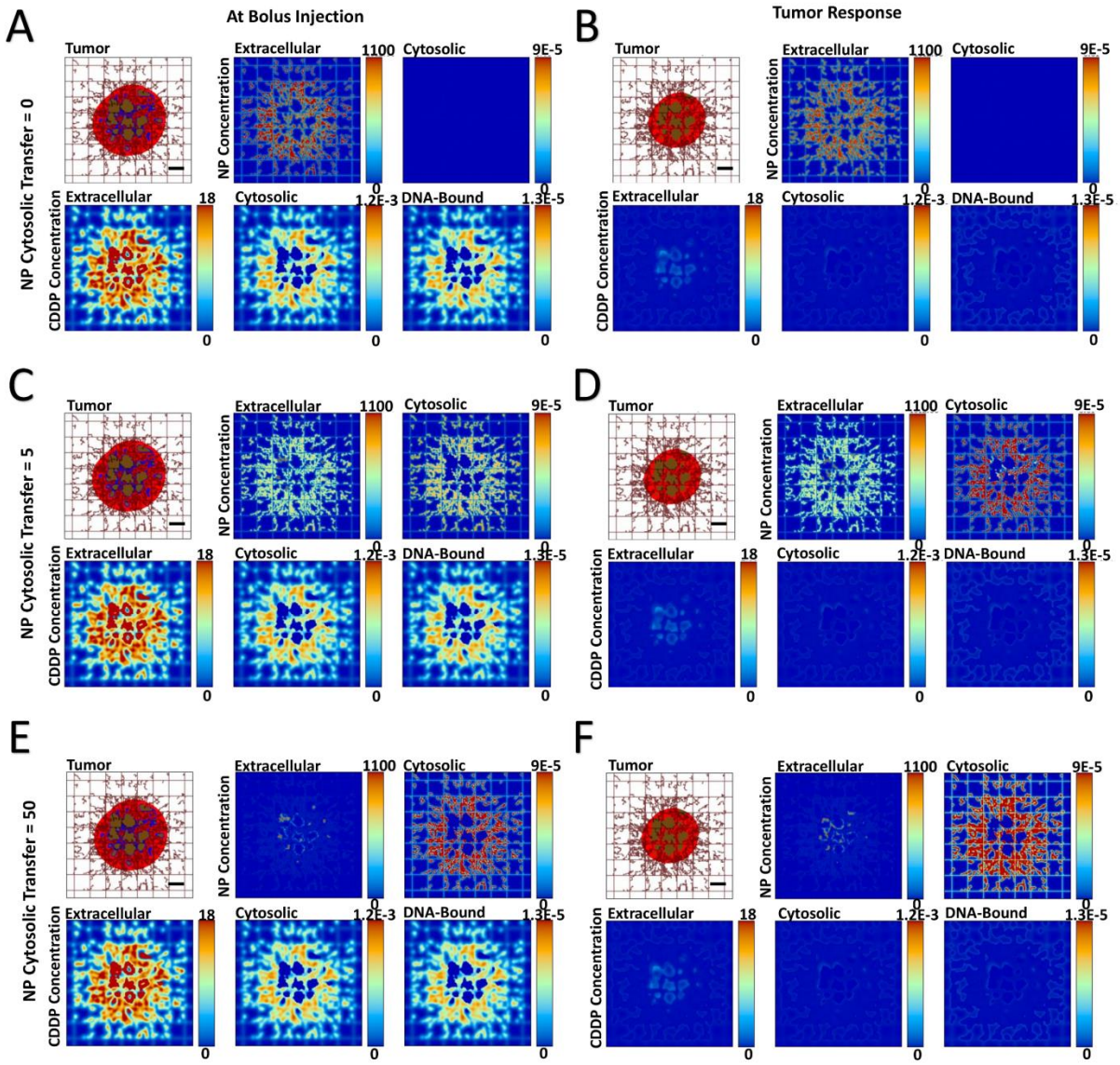
[b]Department of Bioengineering, University of Louisville, Louisville, KY, USA

[c]James Graham Brown Cancer Center, University of Louisville, Louisville, KY, USA

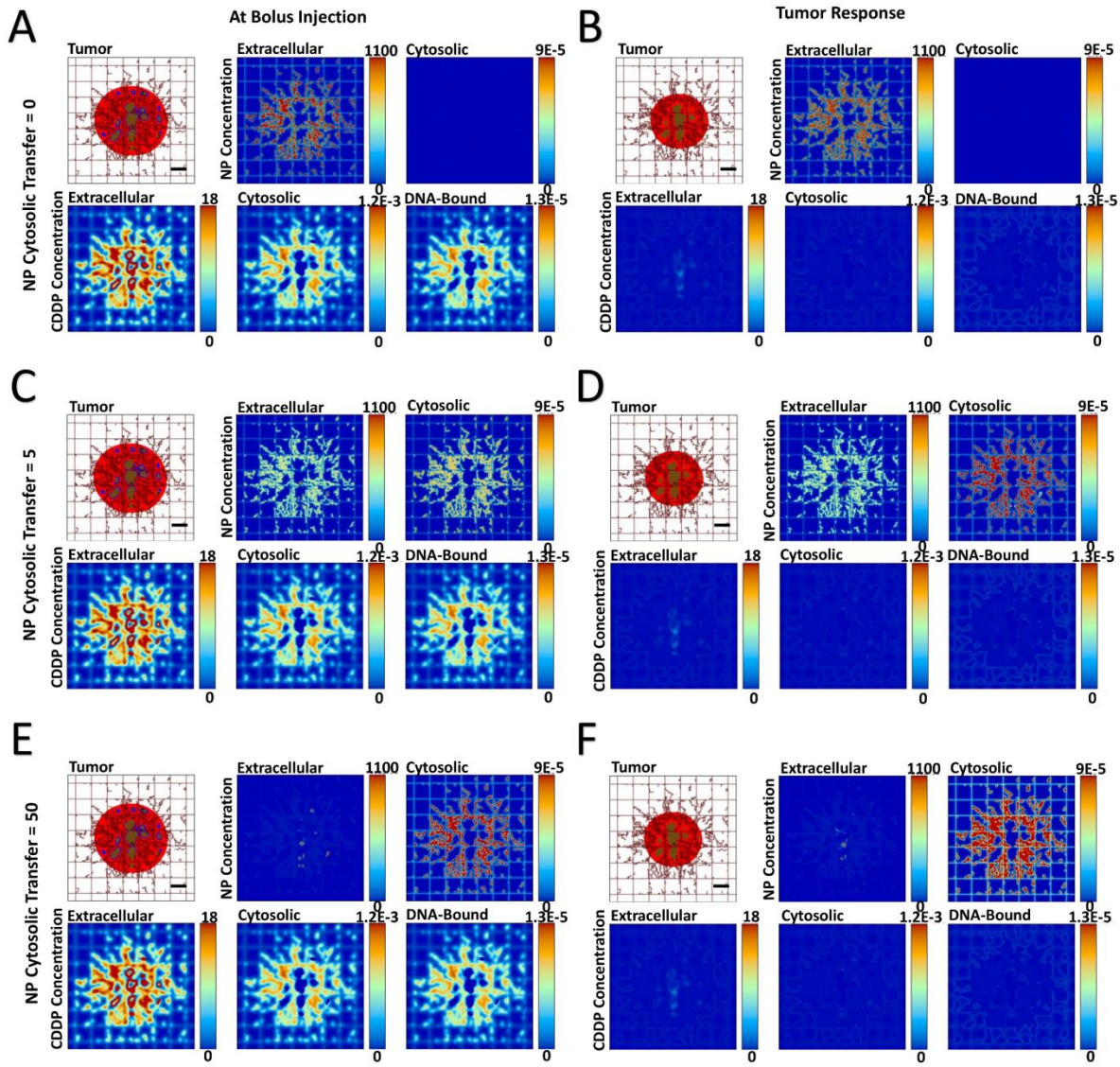
[d]Center for Predictive Medicine, University of Louisville, Louisville, KY, USA

*** Correspondence:** Hermann B. Frieboes, Department of Bioengineering, Lutz Hall 419, University of Louisville, KY 40292, USA. Tel.: 502-852-3302; Fax: 502-852-6806; E-mail: hbfrie01@louisville.edu

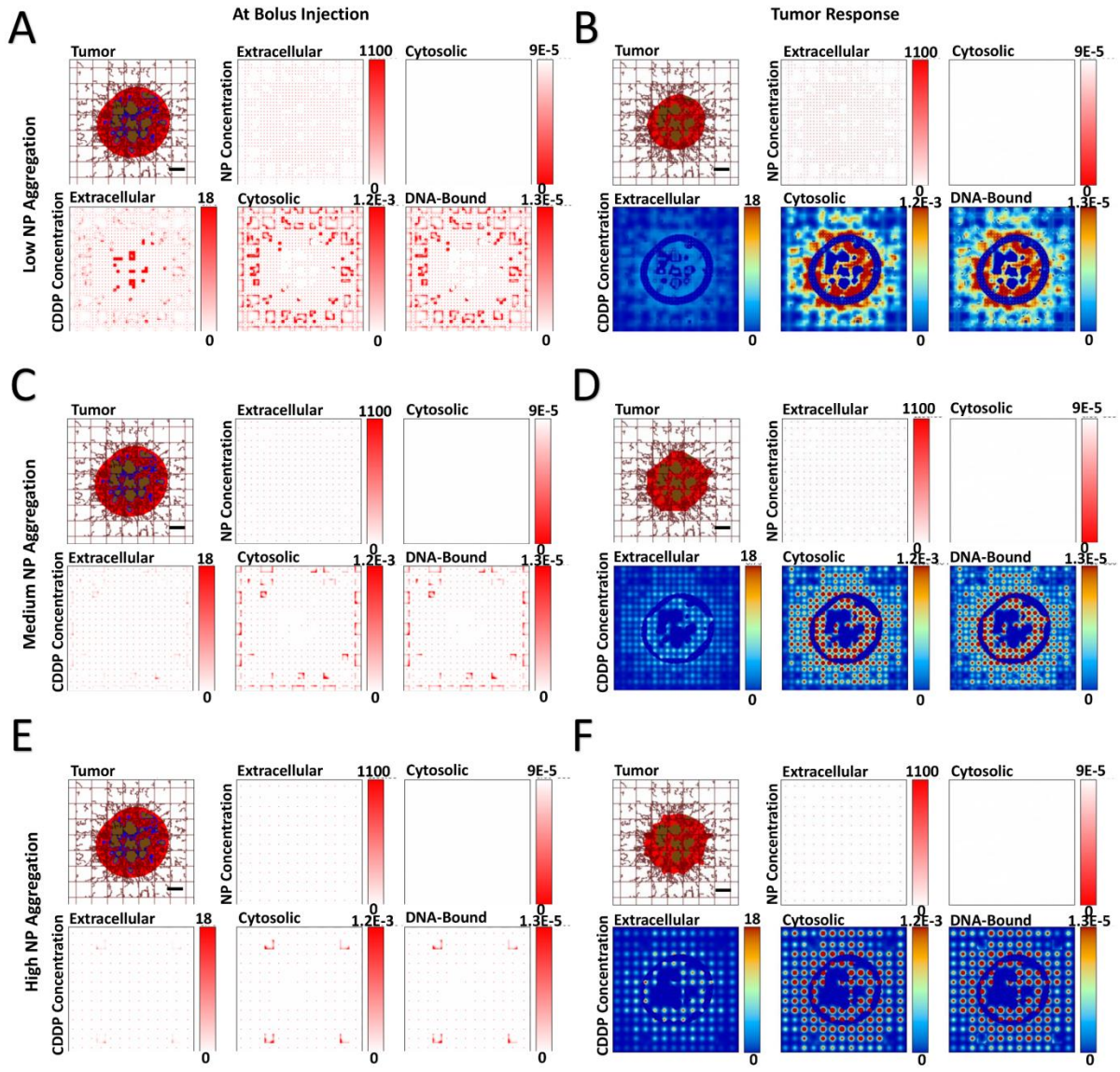
## Supplementary Figures



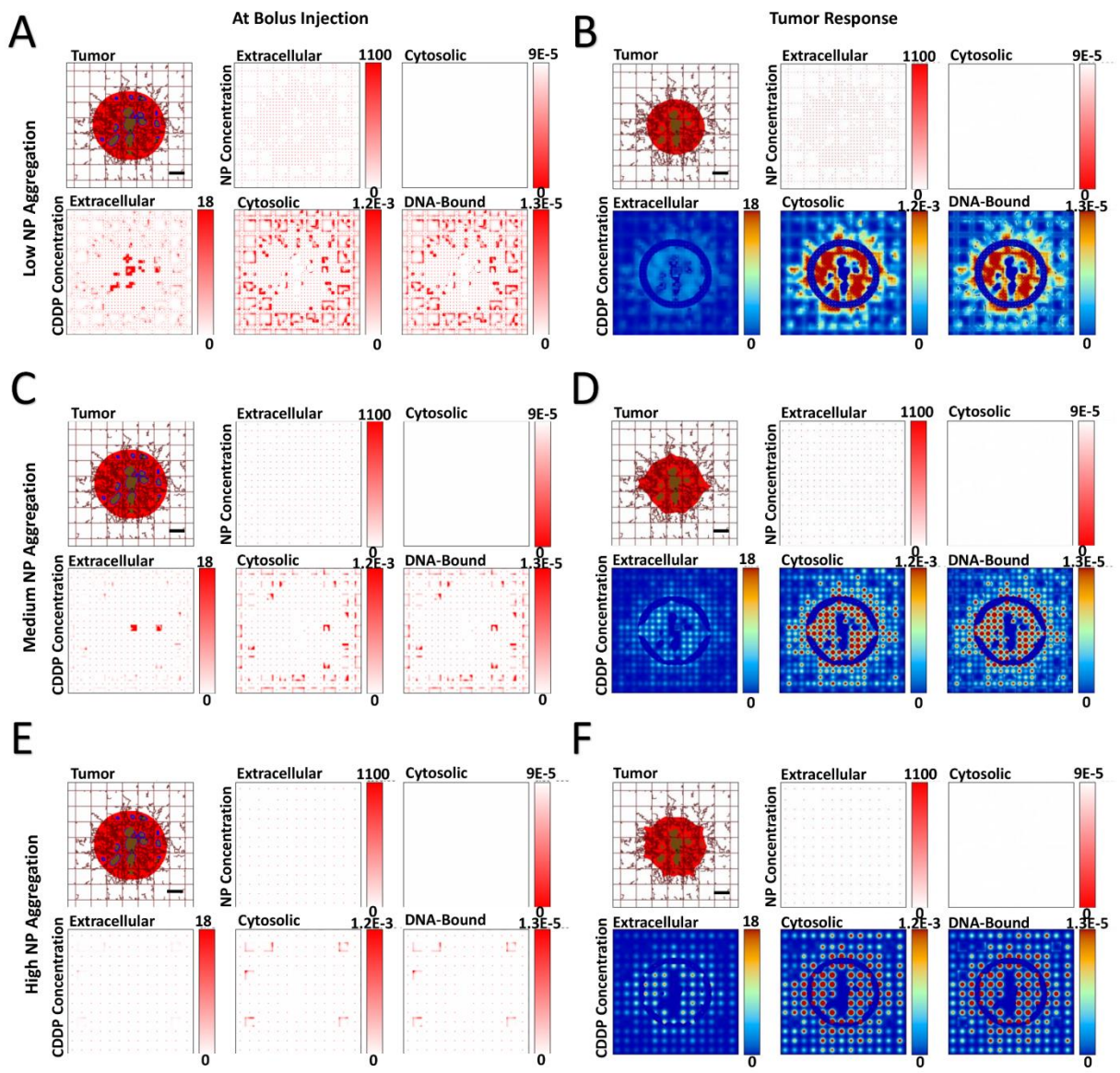

**Supplementary Figure 1** – **Variation of NP cytosolic transfer for tumor lesion of MEDIUM vascular heterogeneity**, showing spatial distribution of PLGA NPs and cisplatin (CDDP) in the three compartments of the model. The NP cytosolic transfer coefficient was varied from low (=0), medium (=5), and high (=50) values. Images are from the first output interval immediately after bolus injection of CDDP-loaded NPs (**Panels A, C, E**) and the second output interval after the drug has taken effect (**Panels B, D, F**). The top left figure in each panel depicts the tumor (red: proliferating tissue; blue: hypoxic tissue; brown: necrotic tissue) along with surrounding capillary network (brown lines). Pre-existent (normal) vasculature is shown as a regular rectangular grid and neo-vasculature induced by angiogenesis is shown as irregular lines. Drug concentration is shown for extracellular (μM), cytosolic (Fmol x hr), and DNA-bound (Fmol x hr) compartments. Bar = 250 μm.




**Supplementary Figure 2** – **Variation of NP cytosolic transfer for tumor lesion of LOW vascular heterogeneity**, showing spatial distribution of PLGA NPs and cisplatin (CDDP) in the three compartments of the model. The NP cytosolic transfer coefficient was varied from low (=0), medium (=5), and high (=50) values. Images are from the first output interval immediately after bolus injection of CDDP-loaded NPs (**Panels A, C, E**) and the second output interval after the drug has taken effect (**Panels B, D, F**). Drug concentration is shown for extracellular (μM), cytosolic (Fmol x hr), and DNA-bound (Fmol x hr) compartments. Colors are as in **Supplementary Figure 1**. Bar = 250 μm.




**Supplementary Figure 3** – **Variation of NP aggregation for tumor lesion of MEDIUM vascular heterogeneity**, showing spatial distribution of PLGA NPs and cisplatin (CDDP) in the three compartments of the model. NP aggregation was varied from low (5x5 blocks), medium (10x10 blocks), and high (15x15 blocks). Images are from the first output interval (immediately after bolus injection of CDDP-loaded NPs (**Panels A, C, E**) and the second output interval (after the drug has taken effect (**Panels B, D, F**). Drug concentration is shown for extracellular (μM), cytosolic (Fmol x hr), and DNA-bound (Fmol x hr) compartments. Colors are as in **Supplementary Figure 1**. Bar = 250 μm.




**Supplementary Figure 4** – **Variation of NP aggregation for tumor lesion of LOW vascular heterogeneity**, showing spatial distribution of PLGA NPs and cisplatin (CDDP) in the three compartments of the model. NP aggregation was varied from low (5x5 blocks), medium (10x10 blocks), and high (15x15 blocks). Images are from the first output interval (immediately after bolus injection of CDDP-loaded NPs (**Panels A, C, E**) and the second output interval (after the drug has taken effect (**Panels B, D, F**). Drug concentration is shown for extracellular (μM), cytosolic (Fmol x hr), and DNA-bound (Fmol x hr) compartments. Colors are as in **Supplementary Figure 1**. Bar = 250 μm.