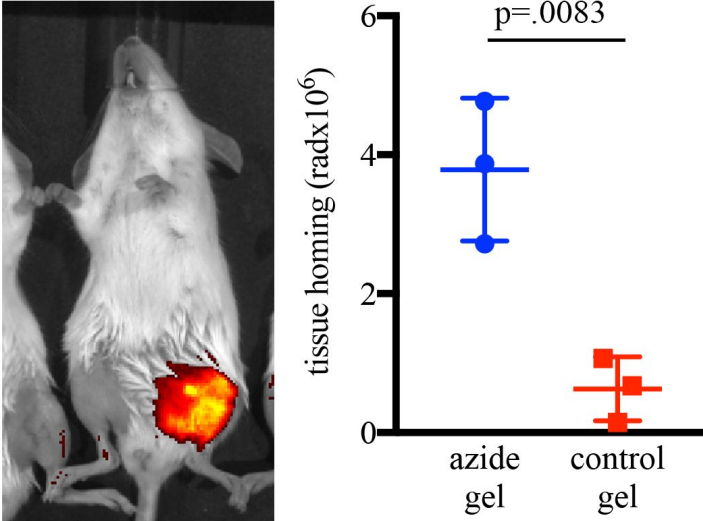
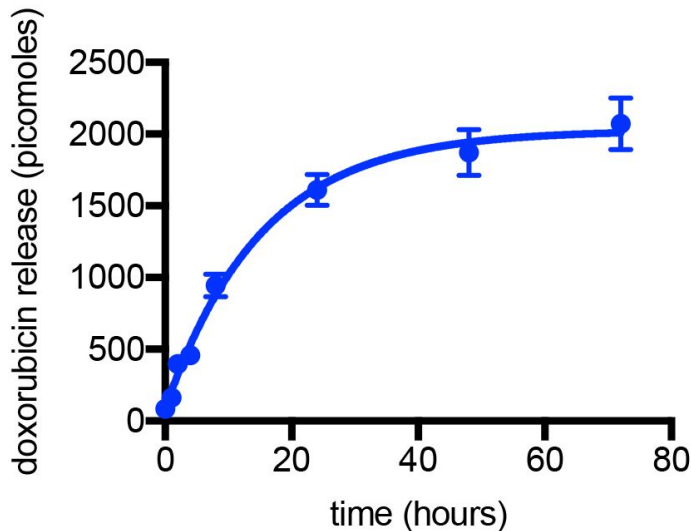


**Supplemental Information:**



Supplemental Figure 1: Click chemistry-mediated targeting of orally-administered drug surrogates to intramuscular gels. Mice were injected intramuscularly with azide-conjugated and unconjugated hydrogels. Targeting to these gels was tested through administration of oral gavage of fluorescently-labeled DBCO groups. A) representative IVIS images and B) quantification of fluorescence at gel site. Values represent mean  $\pm$  SEM,  $n=3$ .  $p$ -value from Student's two-tailed  $t$ -test (homoscedastic).



**Supplemental Figure 2:** Sustained release of doxorubicin after conjugating of doxorubicin prodrug to azide-alginate.

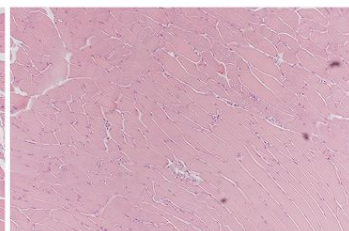
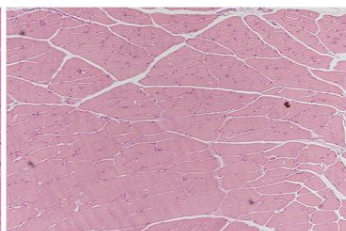
**Supplemental Figure 3:** Histology of the major organs three weeks following intramuscular injection of alginate, azide-conjugated alginate or saline. Histology was taken of the injected area (calf) and the heart, kidneys, liver, lung and spleen.

alginate

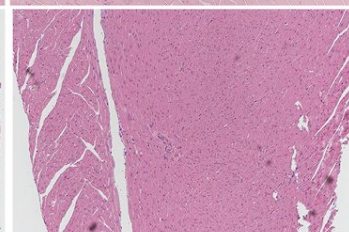
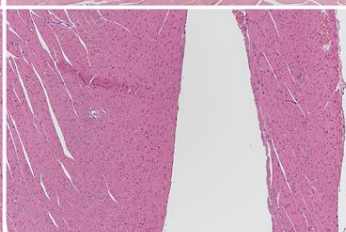
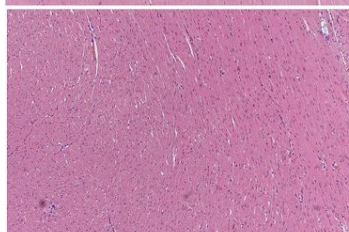
alginate-azide

caline control

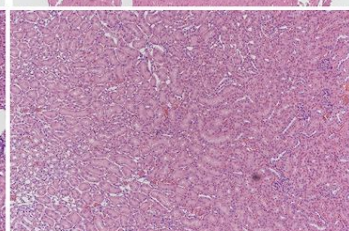
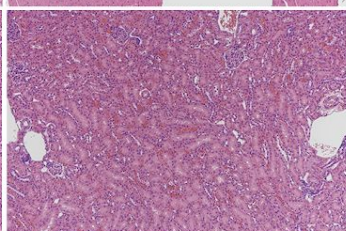
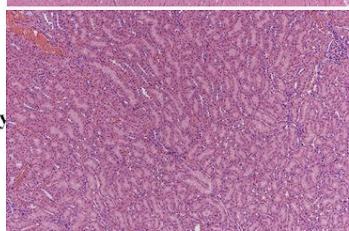
calf



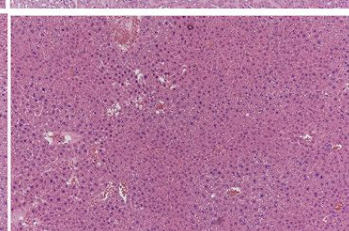
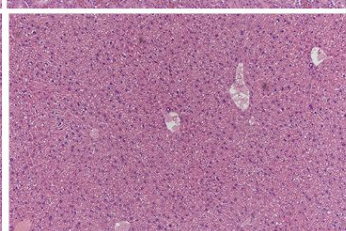
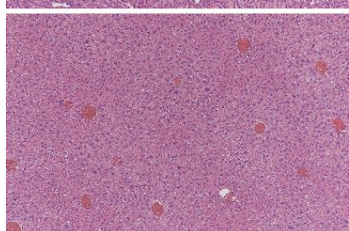
heart



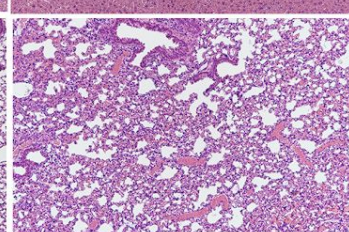
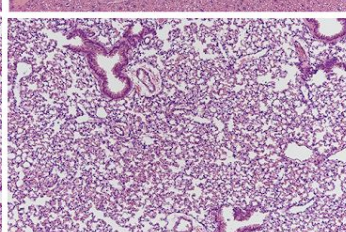
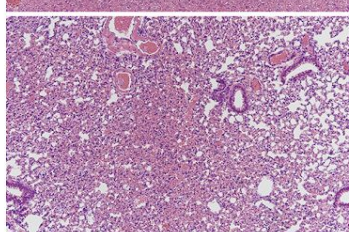
kidney



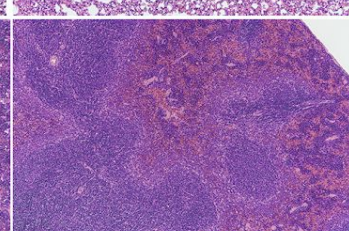
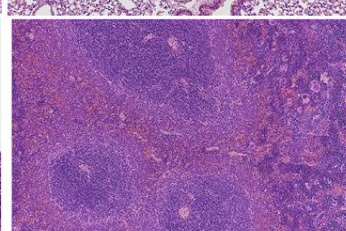
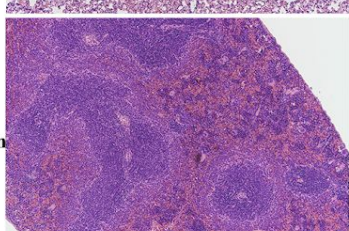
liver



lung



spleen



### **Calculation of theoretical limit to the number of refills.**

The alginate gels injected into the mice (final volume 200uL) consisted of a 1% calcium-crosslinked gel, providing 2mg of alginate or 8 nanomoles of 250,000 Da alginate strands. We measured approximately 200 azides per strand, giving a total number of 1.6 micromoles of azides in the injected material.

For a 23g mouse, 288 nanomoles of prodrug was administered (12.5 micromoles / kg) and assuming a 5% capture rate, 14.4 nanomoles of prodrug is captured at the site. This amount is .9% of the total number of azides, giving a theoretical maximum of 111 refills.