

# Turning tumors into therapeutic drug factories: efficacy across oncology indications

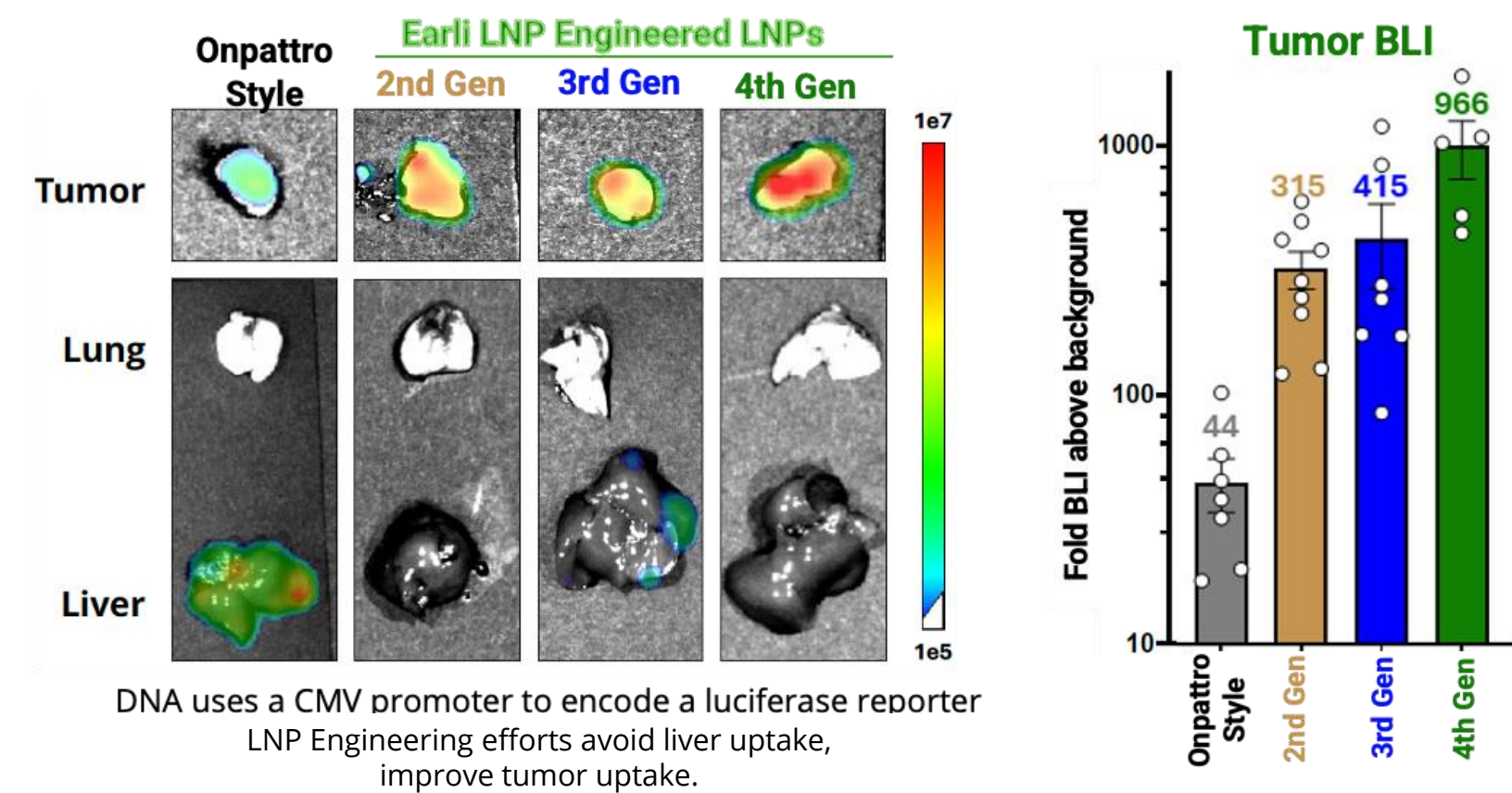
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## Background and Rationale

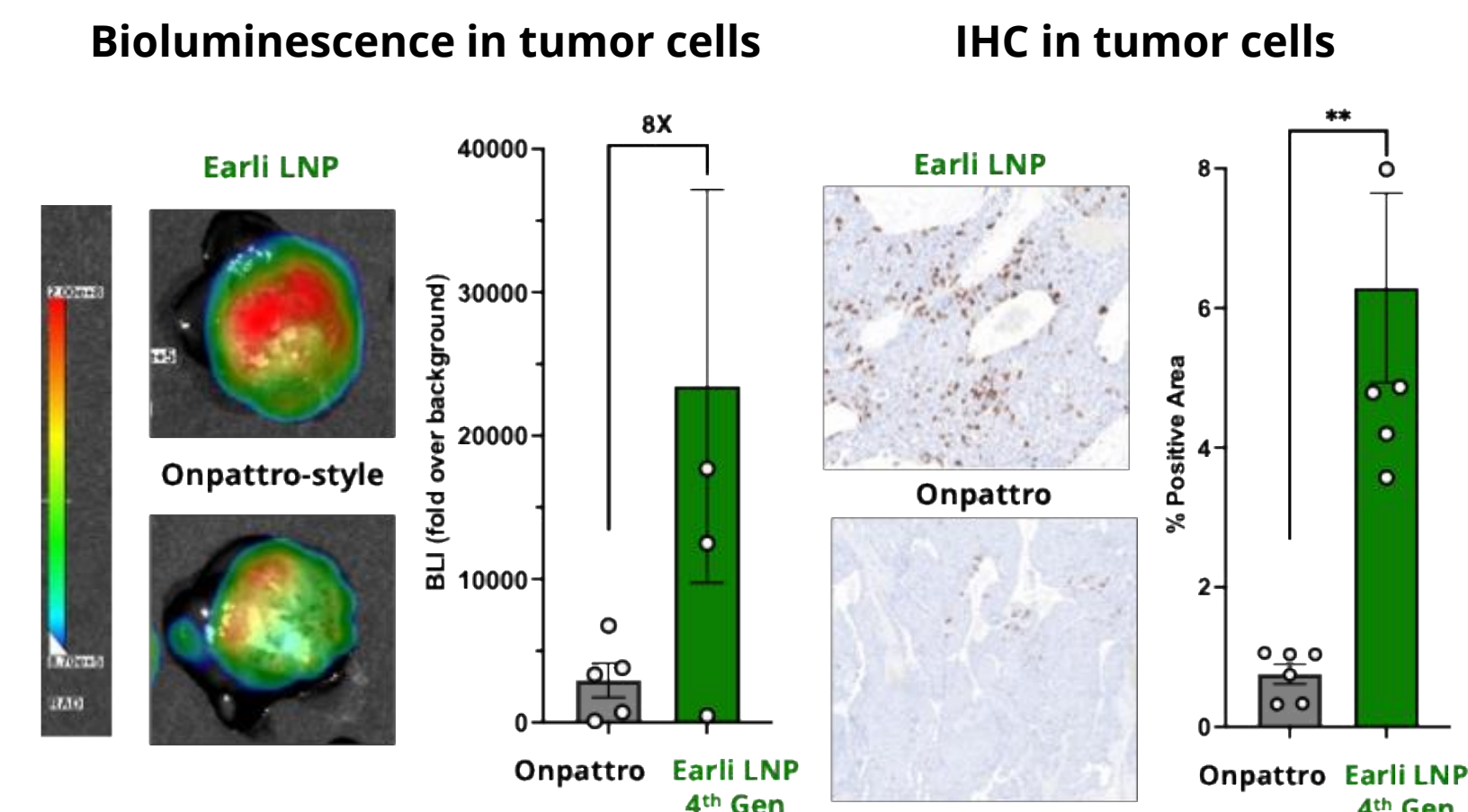
- Although DNA can be used to drive expression of cancer therapeutics, clinical use is often restricted to intratumoral injection due to lack of specificity.
- Earli's cancer-activated expression platform permits broad systemic DNA delivery to a multitude of cancers by using conditionally active promoters to drive potent anti-tumor activity while minimizing systemic toxicity.
- Two orthogonal levels of specificity support this approach:
  1. Lipid nanoparticles (LNP) for extrahepatic delivery of nucleic acids following intravenous (IV) injection to maximize tumor DNA delivery
  2. Highly engineered synthetic cancer-activated promoters (CAP) that restrict expression to malignant cells.
- Net outcome is tumor-localized therapeutic activity with limited systemic exposure, enabling potent efficacy while reducing dose-limiting toxicities

## Earli LNPs have enhanced tumor delivery



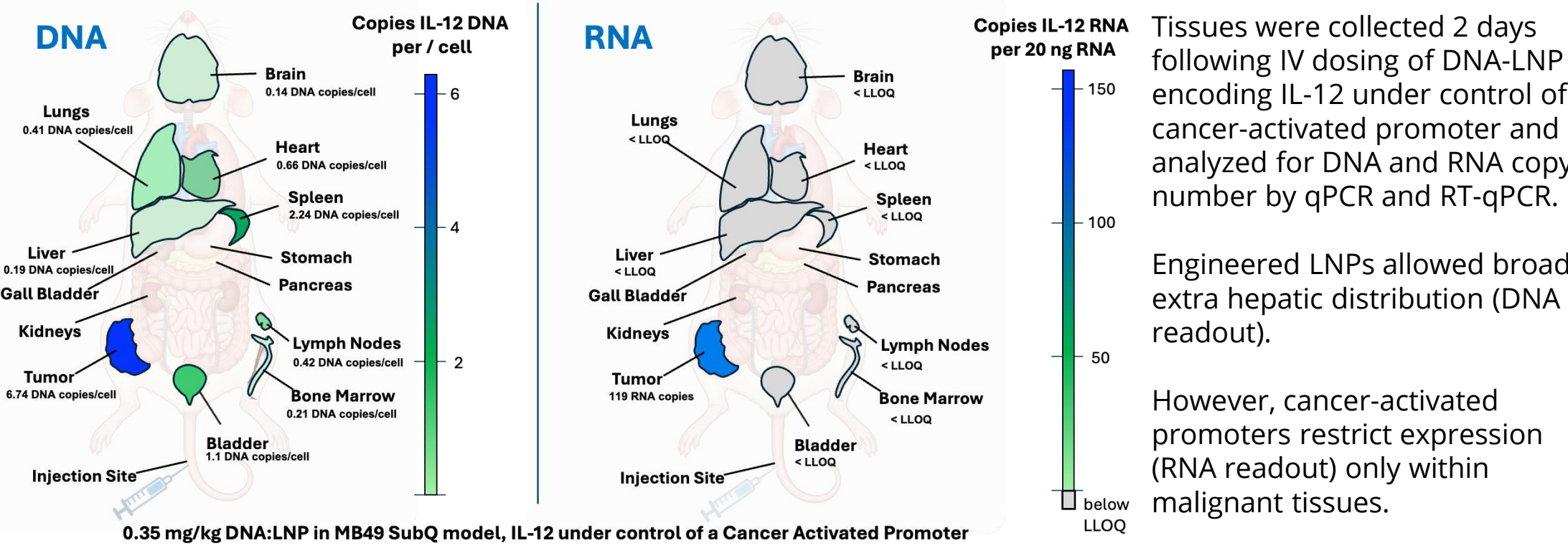
Standard LNPs (e.g., Onpatro) undergo rapid ApoE-mediated hepatic uptake after IV dosing, limiting systemic distribution. Earli's LNPs use modified surface chemistry to evade liver uptake and extend exposure to extrahepatic tissues, including tumors, without active targeting. Right: Biodistribution of IV-dosed Earli LNP/DNA (CAG-luciferase).

## Earli LNPs enhance delivery to orthotopic HCC



LNPs were assessed using a DNA with a CAG promoter driving luciferase in Hep3B liver orthotopic xenograft model. The lead LNP achieved 8-fold higher tumor expression than the same DNA formulated in an LNP used in a commercial siRNA product. Importantly, IHC analysis of the tumored liver using the HA-tagged Fluc also confirmed ~6X increase in the percent transfection area in liver tumors.

## Extra-hepatic distribution with precise cancer specificity

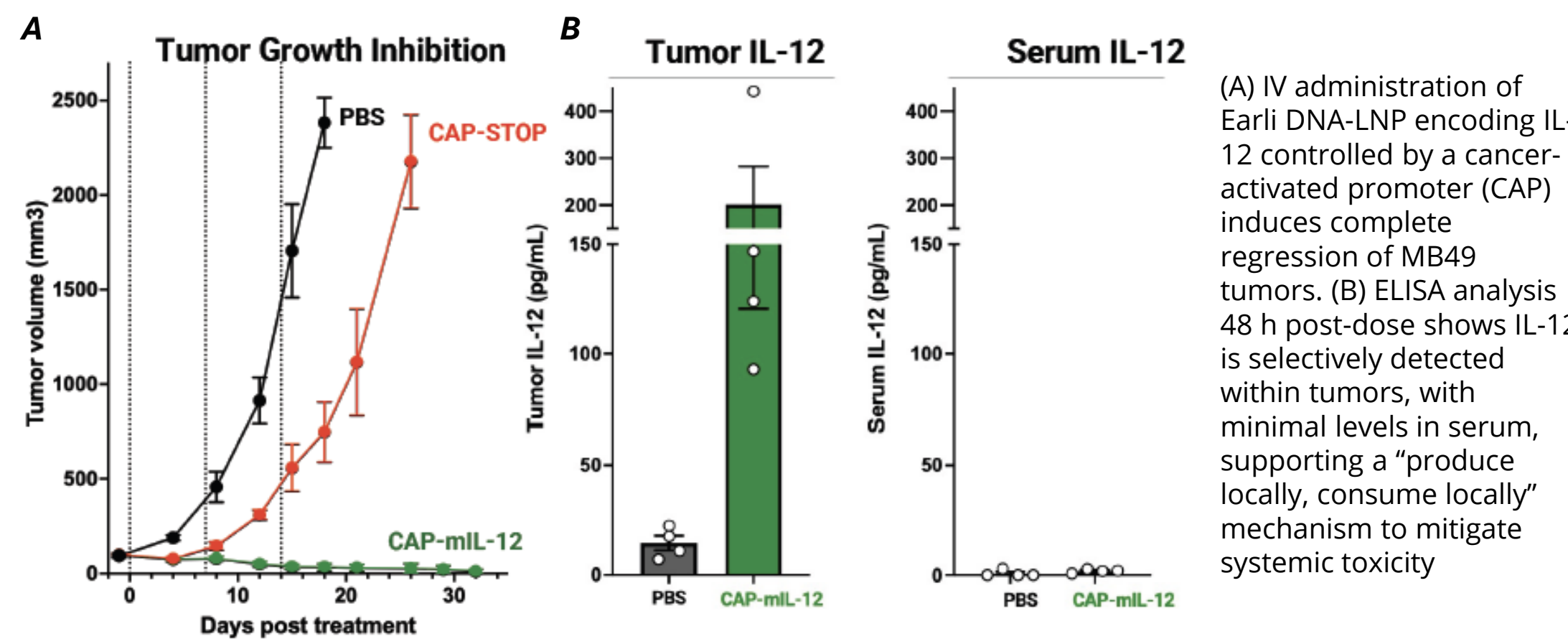


Tissues were collected 2 days following IV dosing of DNA-LNP encoding IL-12 under control of cancer-activated promoter and analyzed for DNA and RNA copy number by qPCR and RT-qPCR.

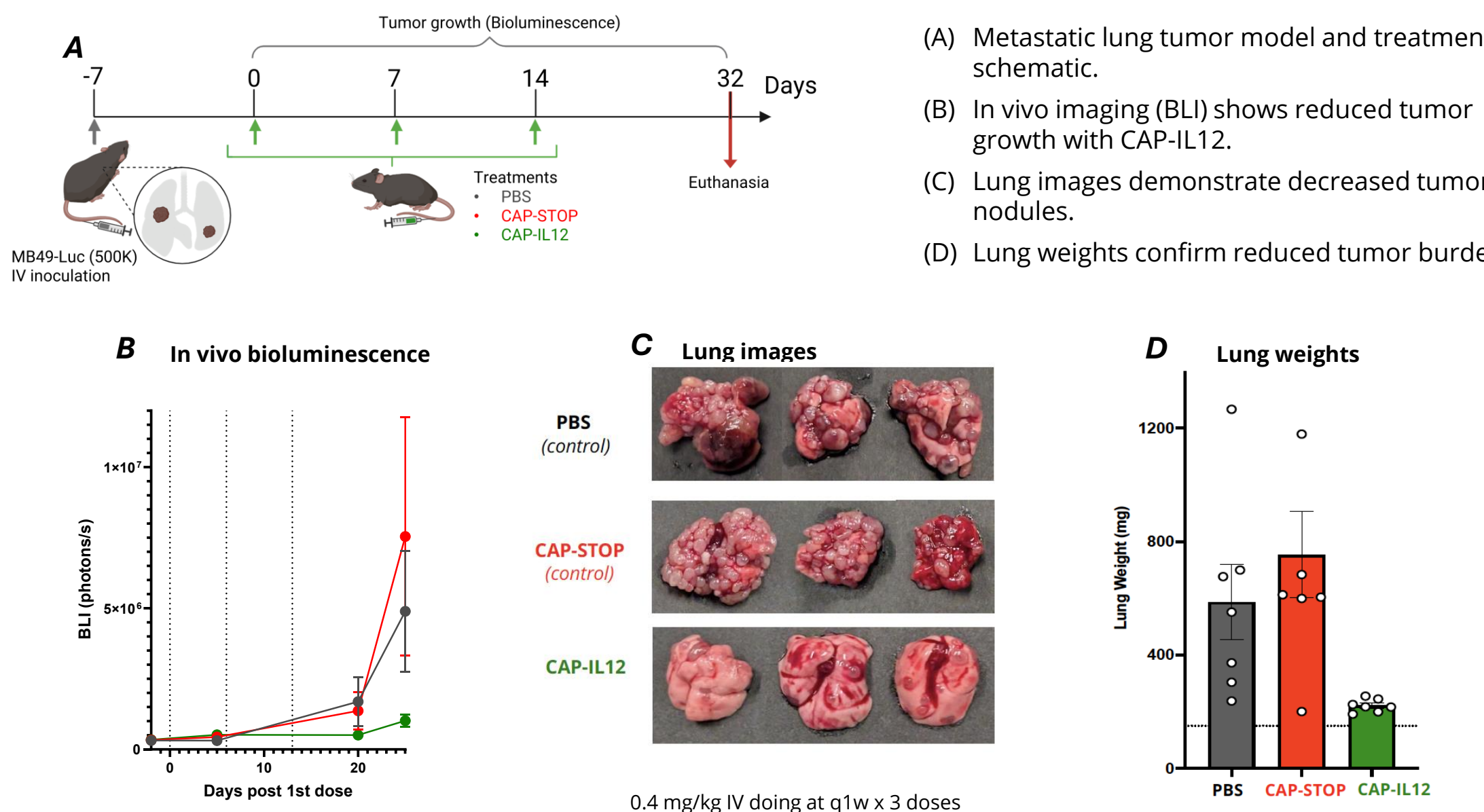
Engineered LNPs allowed broad, extra hepatic distribution (DNA readout).

However, cancer-activated promoters restrict expression (RNA readout) only within malignant tissues.

## Cancer-activated expression of IL-12 leads to complete regression of MB49 subcutaneous tumors

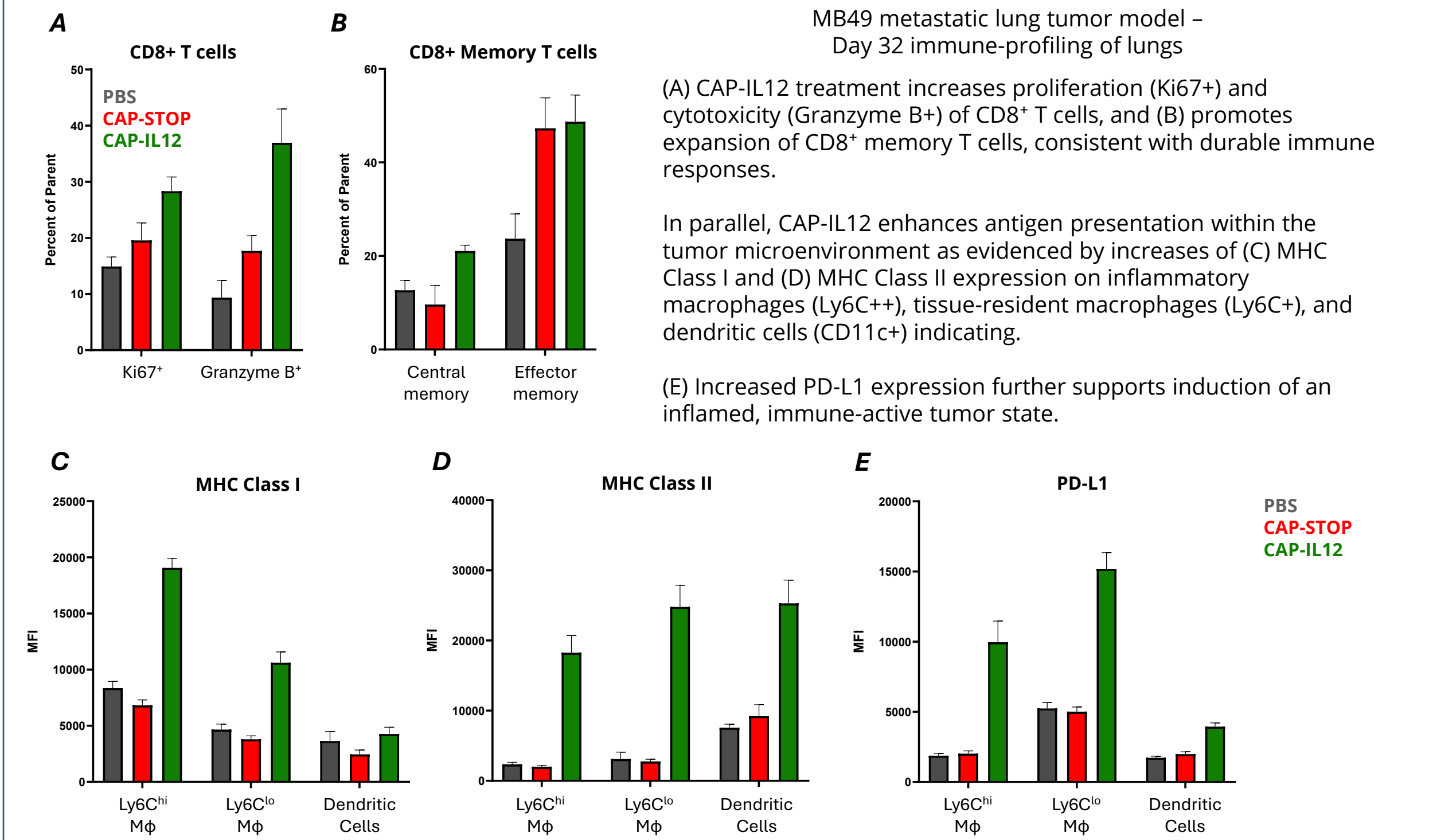


## Cancer-activated expression of IL-12 controls growth of aggressive metastatic lung tumors in mice

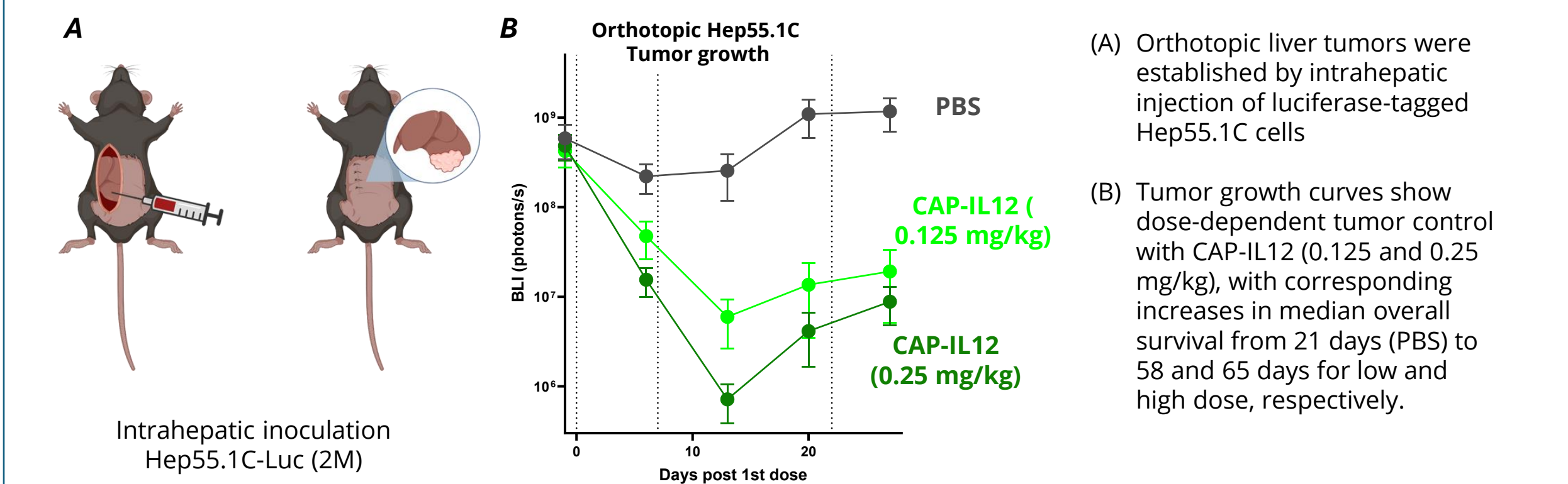


- Metastatic lung tumor model and treatment schematic.
- In vivo imaging (BLI) shows reduced tumor growth with CAP-IL12.
- Lung images demonstrate decreased tumor nodules.
- Lung weights confirm reduced tumor burden.

## CAP-IL12 induces robust CD8 T cell and myeloid activation in lung tumors



## CAP-IL12 reduces orthotopic liver tumor growth



## Conclusions and Next Steps

- ❖ When combined with LNPs that have been engineered for robust extrahepatic delivery, the Earli cancer-activated expression platform delivers highly potent treatments directly at where it is needed while avoiding systemic toxicity enabling systemic administration of DNA therapeutics.
- ❖ Tumor-localized expression minimizes systemic exposure, supporting an improved therapeutic index for cytokine-based therapies, which have been plagued by dose-limiting toxicities.
- ❖ CAP-IL12 drives potent, localized anti-tumor activity, including complete regression and tumor control across multiple models (subcutaneous, metastatic lung, orthotopic liver).
- ❖ CAP-IL12 used localized expression to induce robust intratumoral immune activation, including CD8<sup>+</sup> T cell expansion, memory formation, and enhanced antigen presentation
- ❖ Collectively, these data support broad applicability of Earli's cancer-activated platform across oncologic indications

