

A NIS-based Platform for Quantitative Analysis of Small-Cell Lung Cancer Metastasis



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Introduction

Small-cell lung cancer (SCLC):

- High-grade neuroendocrine carcinoma with poor prognosis
- Rapid proliferative rate, frequent early relapse and high mortality rate
- Early metastatic – already metastatic disease at timepoint of diagnosis
 - ➔ Mechanisms poorly understood

Key challenges for molecular characterization:

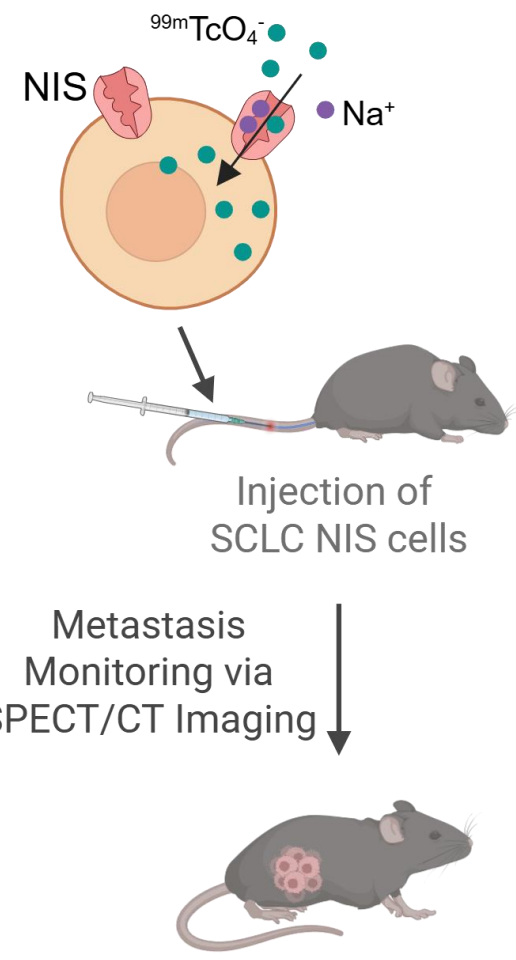
- Limited metastatic patient samples available
- Lack of faithful preclinical models and limited sensitivity of metastasis detection *in vivo*

Quantitatively assess metastatic spread and underlying biological mechanisms

- ➔ NIS-reporter gene imaging via single-photon emission computed tomography (SPECT) and computed tomography (CT)

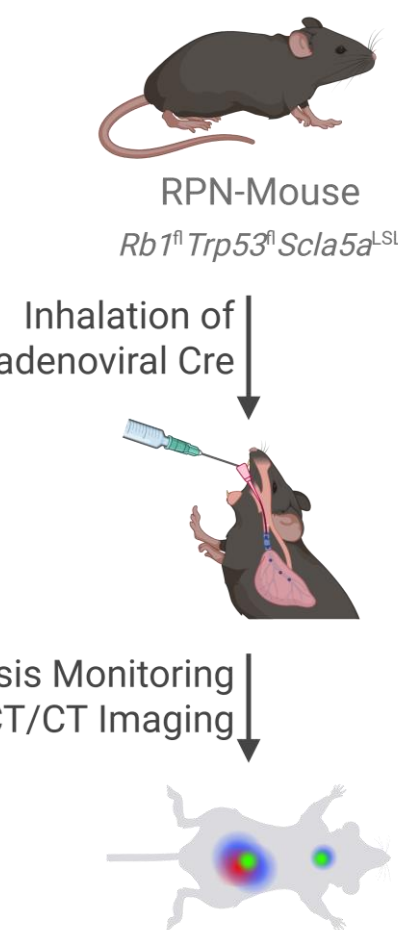
Methods

SCLC metastasis mouse model for functional genomics



- Lentiviral transduction of murine SCLC cells with NIS (*Scla5a*) plasmid
- Generate genetic perturbations
 - *Hox* or *Smad* family gene knock-outs (KO)
- Intravenous injection (4×10^6 cells) into C57BL/6 mice
- Monitoring of tumor development based on uptake of radioactive tracer via SPECT/CT imaging

Autochthonous SCLC mouse model with Cre-inducible NIS



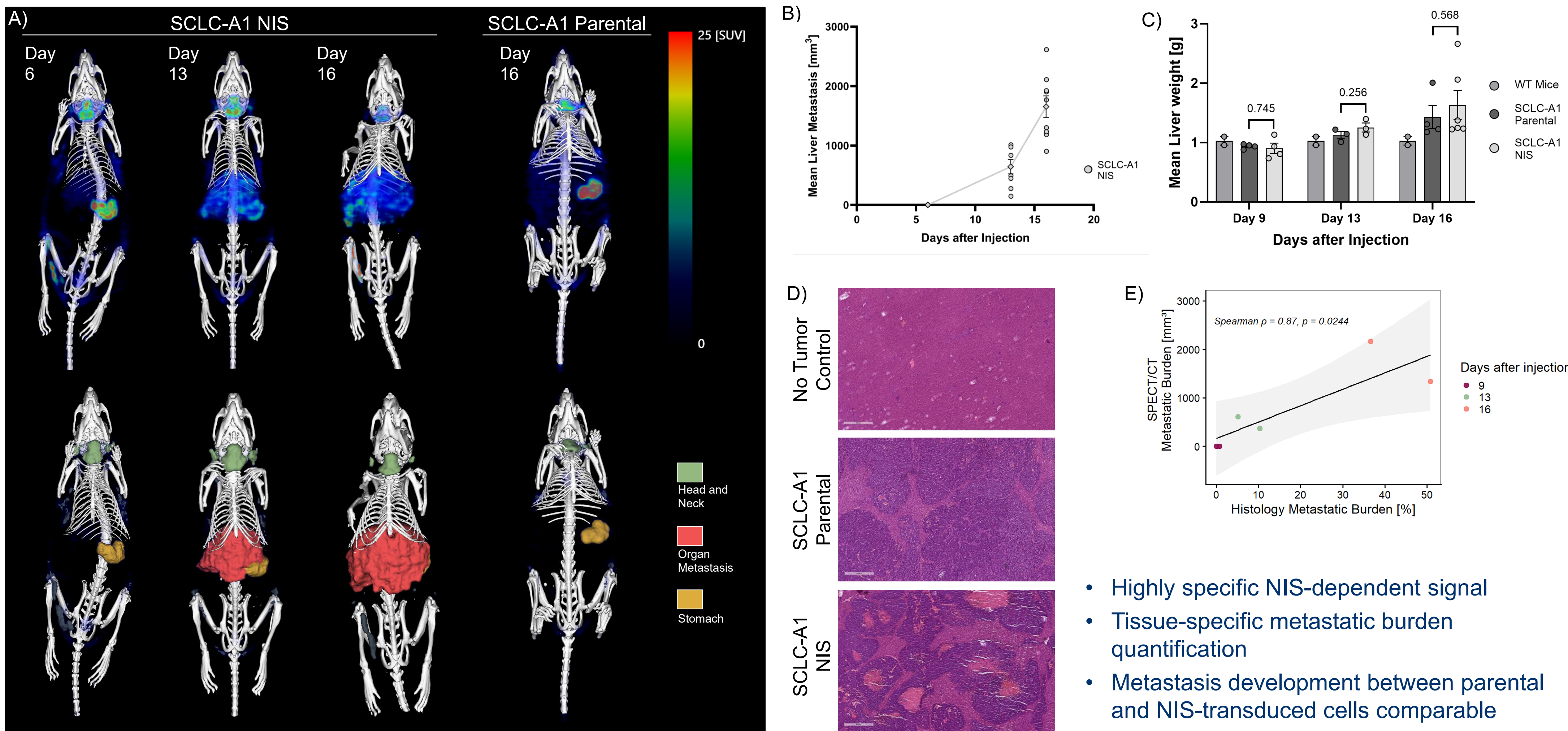
- *Rosa26-LSL-Scla5a* knock-in
- Cre-dependent NIS activation
- Crossing into SCLC genetically engineered mouse model
- Cre-dependent *Rb1*, *Trp53* KO

Imaging and analysis

SPECT/CT nanoScan® Mediso	MRI System 3T Achieva® (T2w) Philips	Segmentation Imalytics® Gremse-IT
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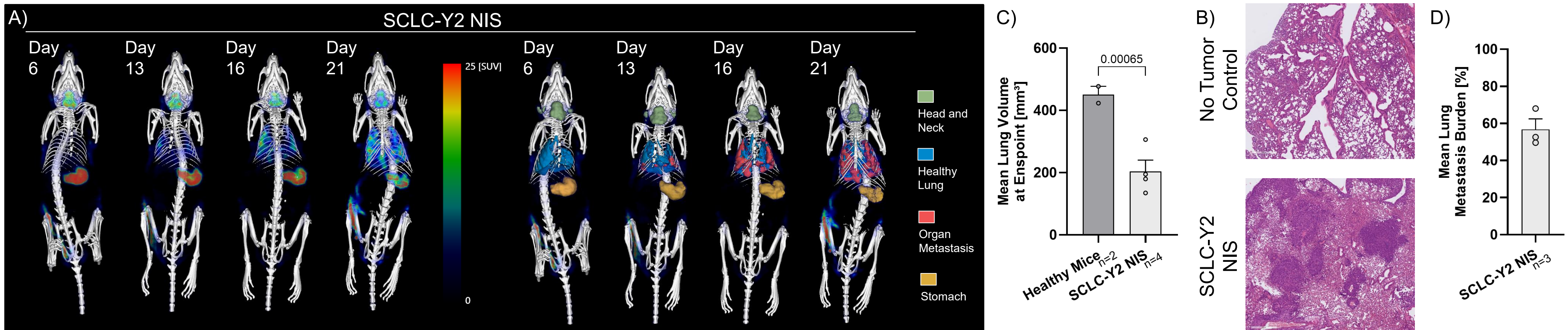
Results

SCLC metastasis visualized by NIS-reporter gene imaging

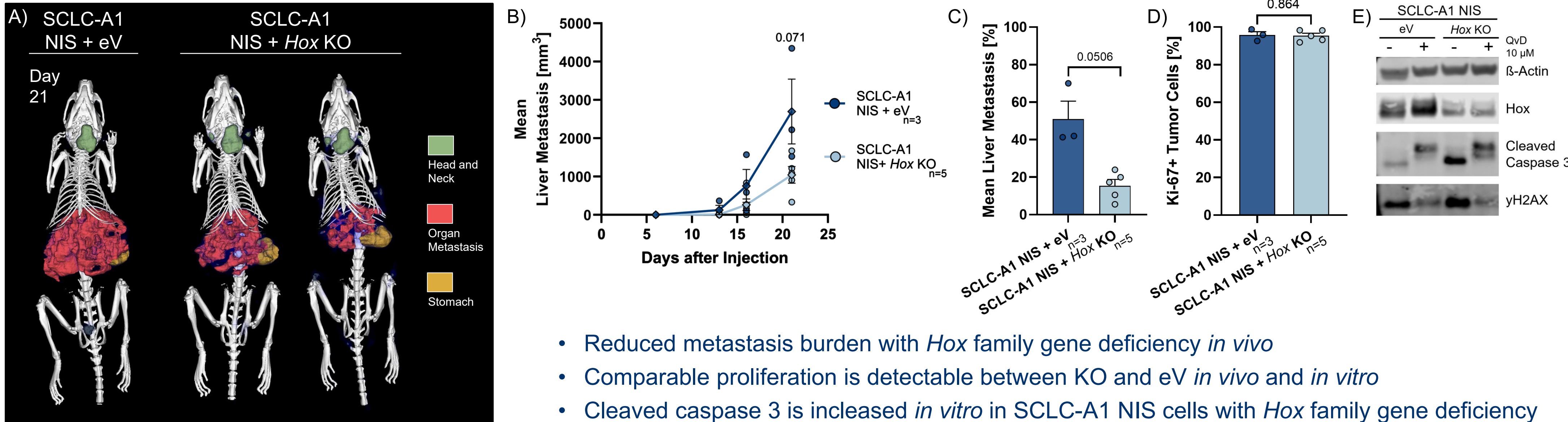


- Highly specific NIS-dependent signal
- Tissue-specific metastatic burden quantification
- Metastasis development between parental and NIS-transduced cells comparable

Various SCLC cell lines differ in metastatic progression and metastasize to different organs



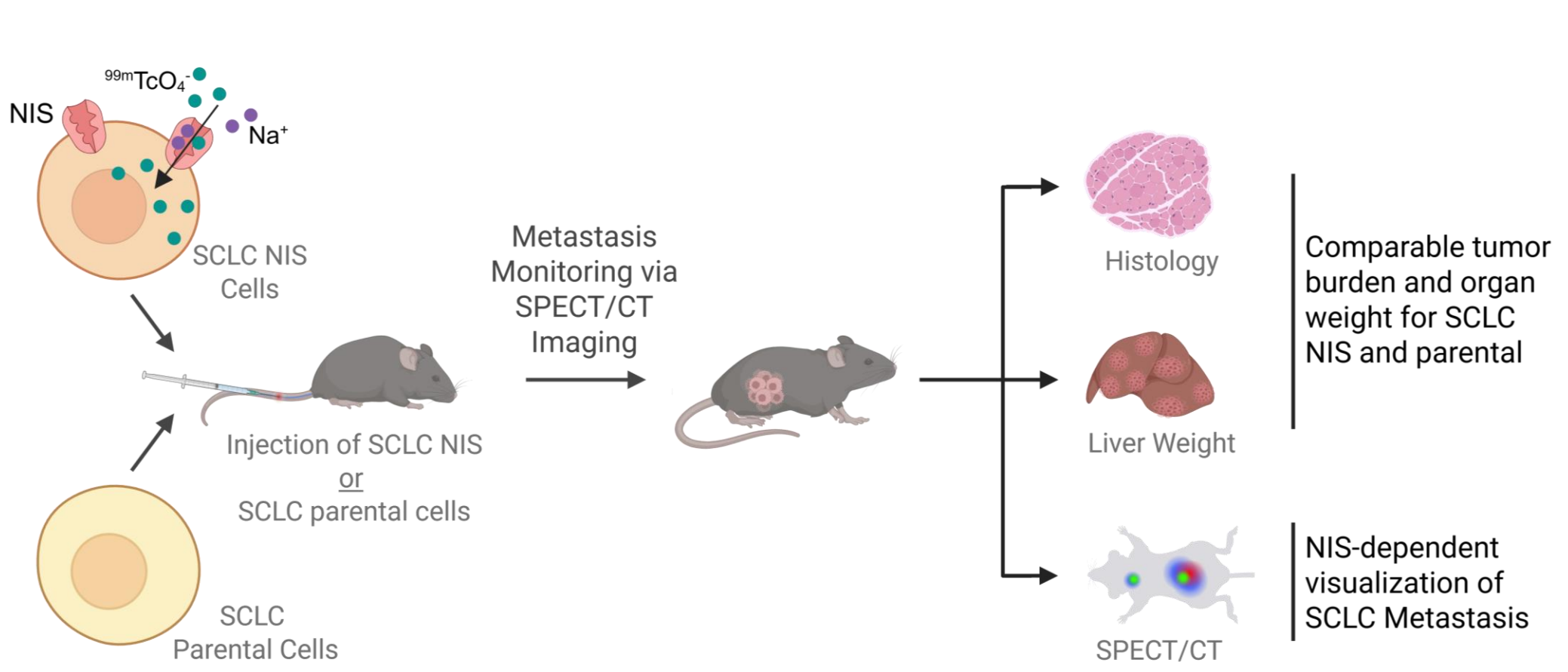
Hox family gene deficiency in SCLC-A1 NIS cells results in decreased metastatic burden in the liver



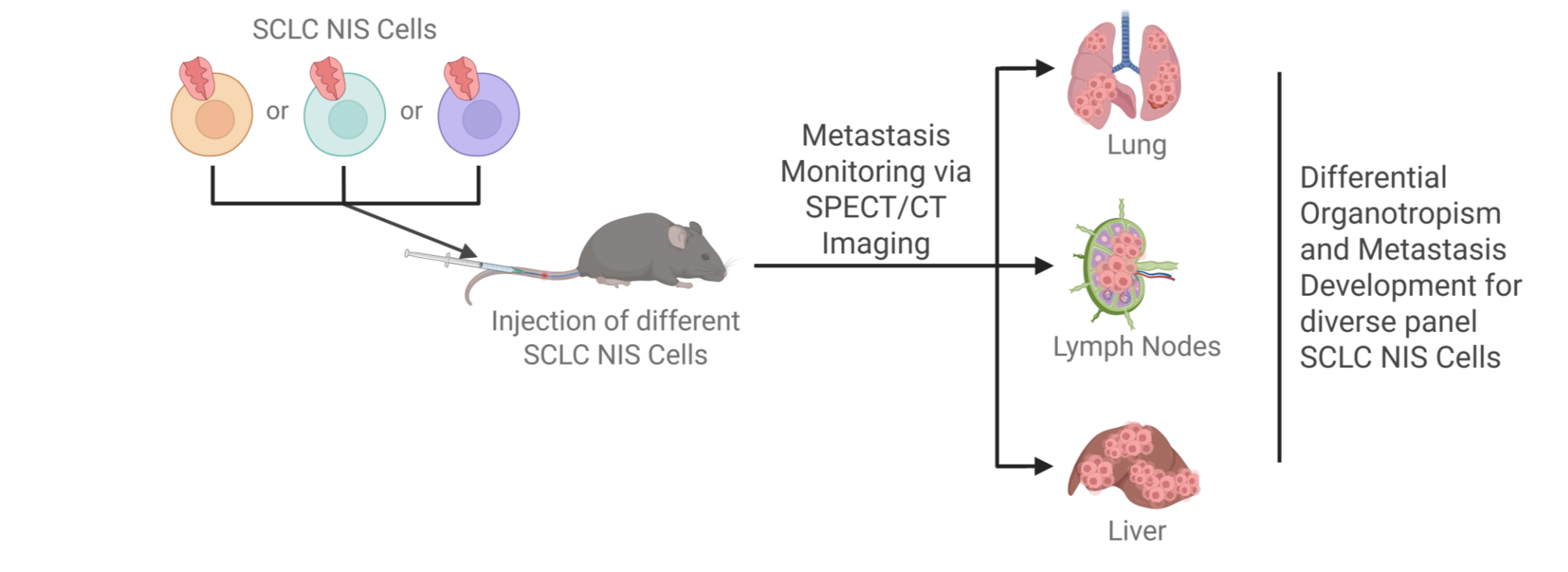
- Reduced metastasis burden with *Hox* family gene deficiency *in vivo*
- Comparable proliferation is detectable between KO and eV *in vivo* and *in vitro*
- Cleaved caspase 3 is increased *in vitro* in SCLC-A1 NIS cells with *Hox* family gene deficiency

Discussion and conclusion

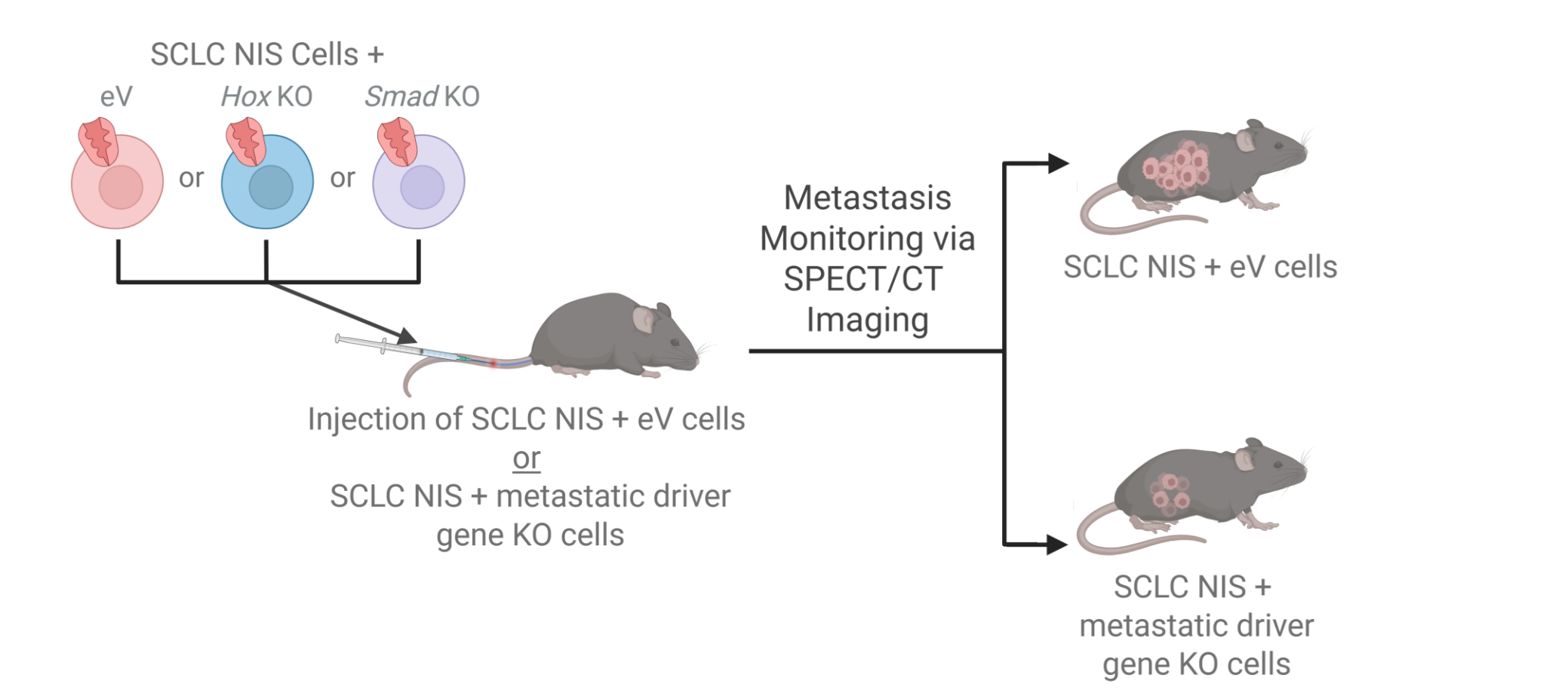
NIS reporter-gene imaging via SPECT/CT established for SCLC



SCLC cells show different organotropisms



Deficiency of drivers reduce metastatic burden



Conclusion and further steps

- Established highly specific NIS-dependent *in vivo* monitoring and quantification method of SCLC metastasis formation via SPECT/CT
 - Allowing detection of differences in tumor burden and differentiation of healthy and metastatic tissue
- Systematic KO of metastasis candidate genes - *Hox* and *Smad* family members under study

Acknowledgments & References

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