

Anti-tumor nucleic acid drug discovery platform



WuXi Biology, Oncology & Immunology Unit

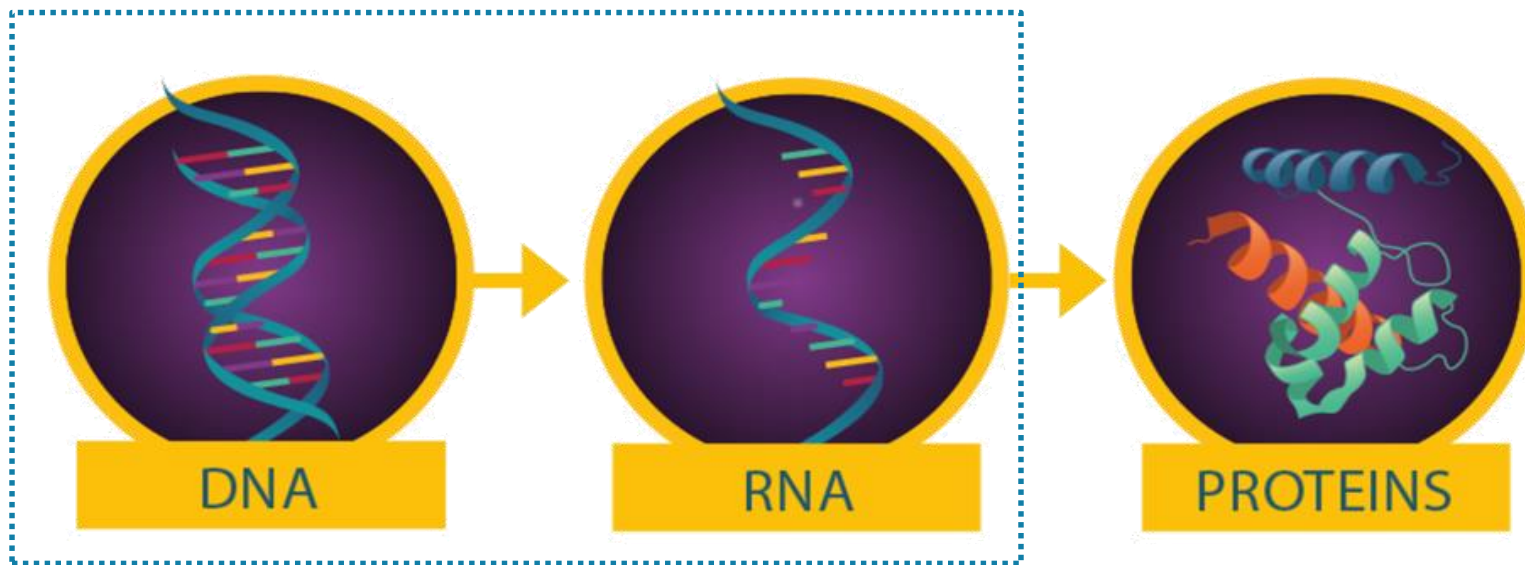


2023.09

Outline

- Introduction of nucleic acid drugs
- History and landscape of nucleic acid drugs
- Consideration for nucleic acid drug evaluation
- Case studies
 - mRNA therapeutics
 - mRNA vaccines

Introduction of nucleic acid drugs



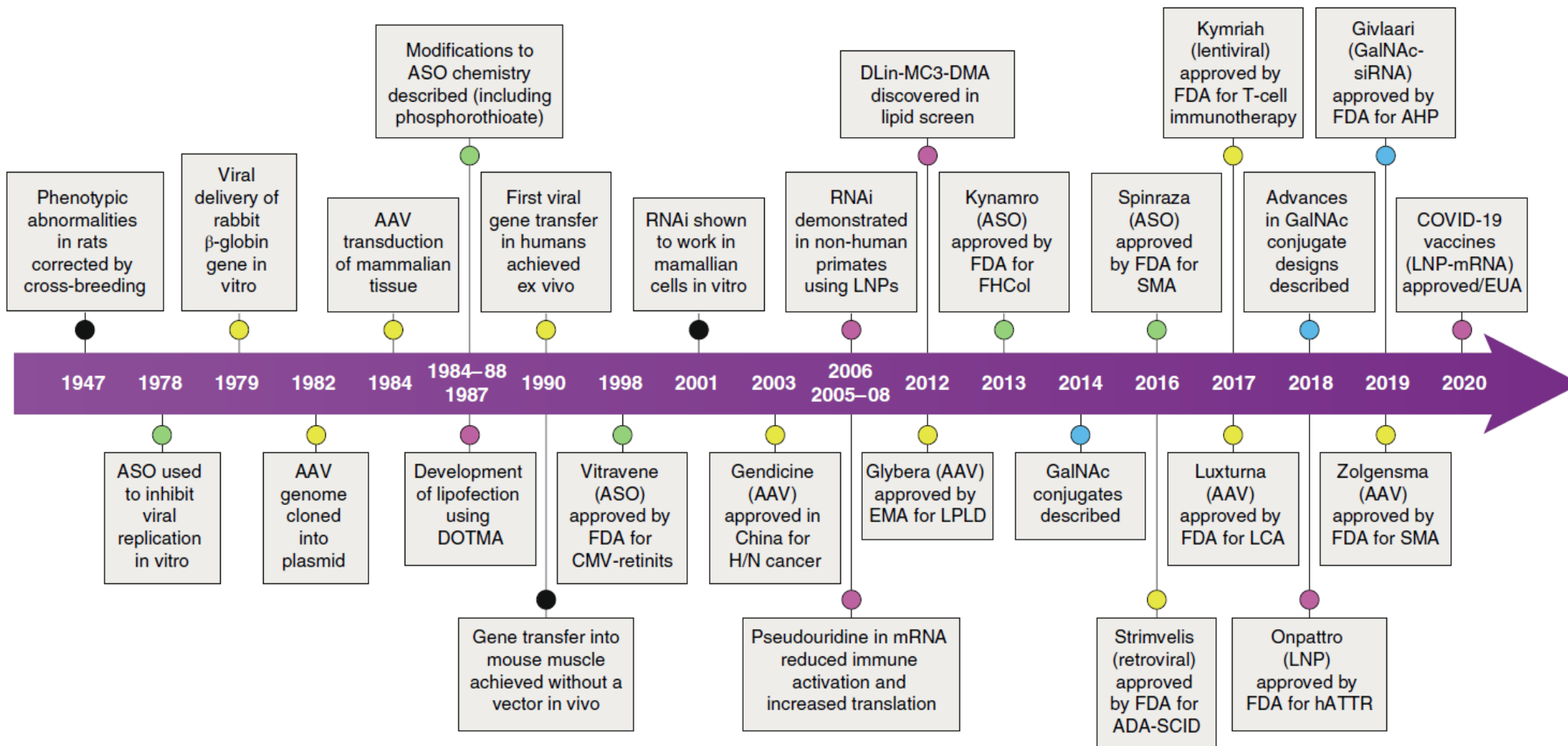
Source: National Cancer Institute

- 1.5% of human genome encodes proteins and only 10-14% of proteins have active binding sites known as ‘druggable’ targets for small molecules.
- Nucleic acid drugs represent a promising arsenal to tackle with these ‘undruggable’ targets.
- Different from recombinant proteins/antibodies, nucleic acid drugs make use of the host translational machinery and thus avoid the limitations during the complicated protein/antibody engineering and manufacture.
- Nucleic acid drugs can target either DNA or RNA. DNA-targeted drugs need to enter nucleus, which raises the concern of host genome integration. By contrast, RNA-targeted drugs mainly function in cytoplasm without such risk.

Classification of nucleic acid drugs (esp. RNA drugs)

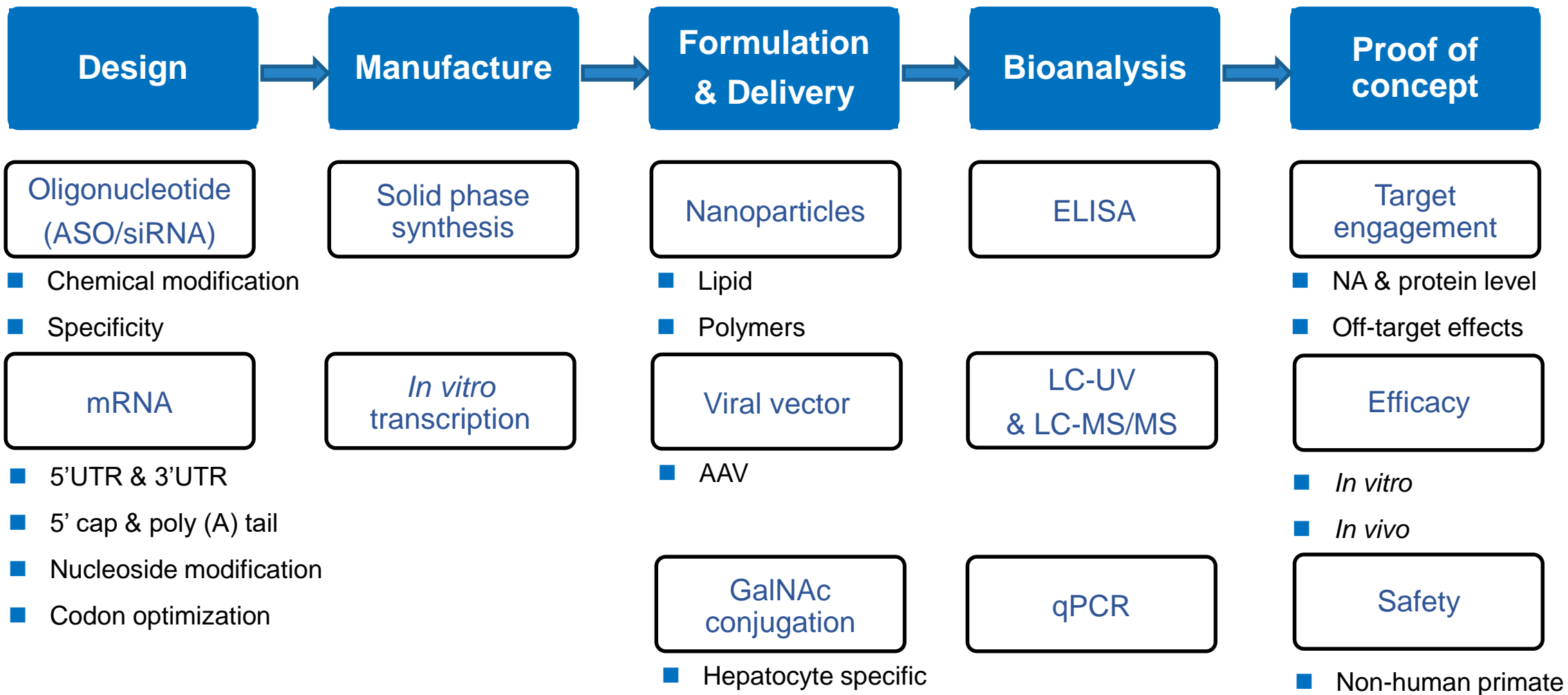
Category		composition	Length	Mechanism
Oligonucleotide	ASO	DNA/RNA	12-30nt (ss)	Regulate protein expression
	siRNA	RNA	20-25nt (ds)	Gene inhibition (gene silence)
	miRNA	RNA	22nt (ss)	Gene inhibition (gene silence)
	Aptamer	DNA/RNA	25-60nt (ss)	Bind receptors
mRNA		RNA		Gene addition (expression target protein)
sgRNA		RNA	17-24nt (ss)	Gene editing

A brief history of nucleic acid drug development



Nat Nanotechnol. 2021 Jun;16(6):630-643.

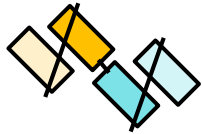
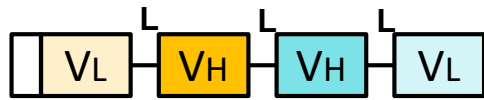
Considerations for nucleic acid drug evaluation



Evaluation of mRNA therapeutics

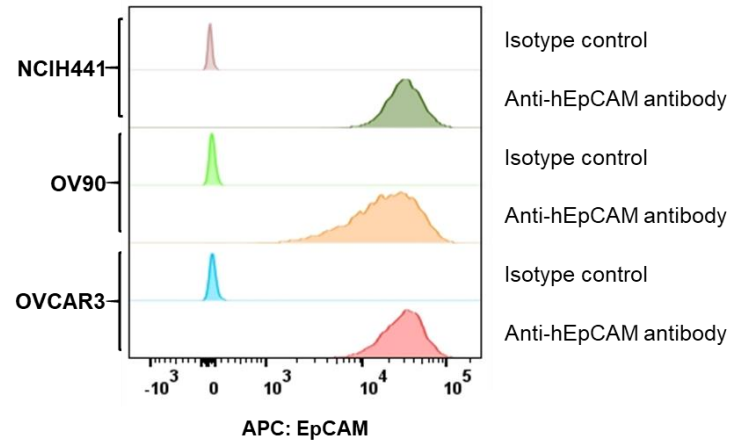
Case study: Target validation, *in vitro* toxicity and dynamics of mRNA-encoded EpCAM-CD3 bispecific antibody

A mRNA-encoded EpCAM targeting bispecifics

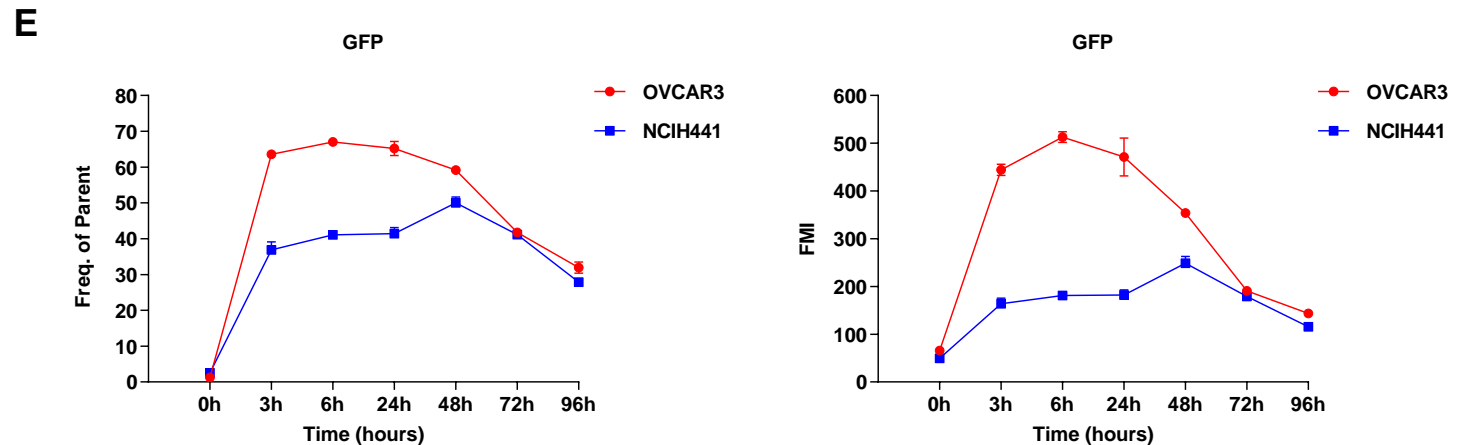
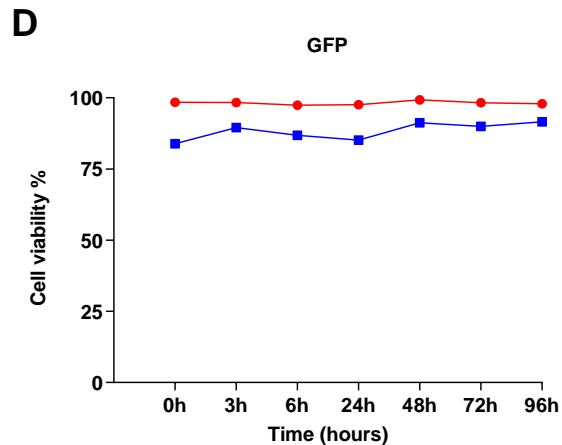
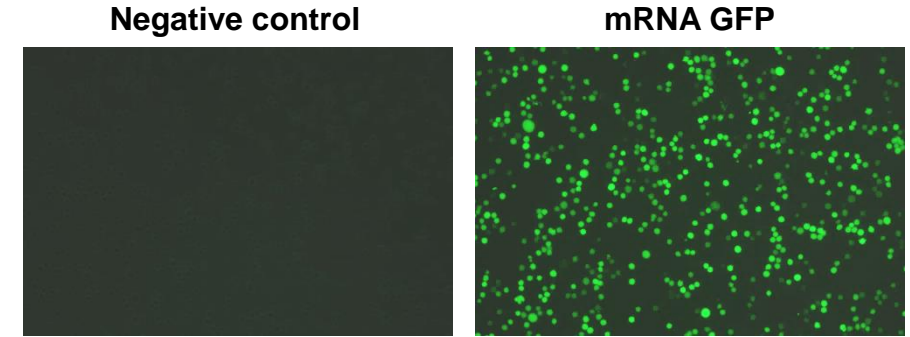


EpCAM (scFv) X CD3 (scFv)

B EpCAM surface expression on tumor cells



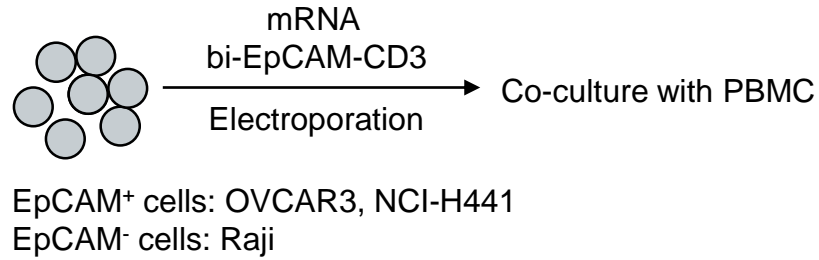
C Transfection efficiency validation



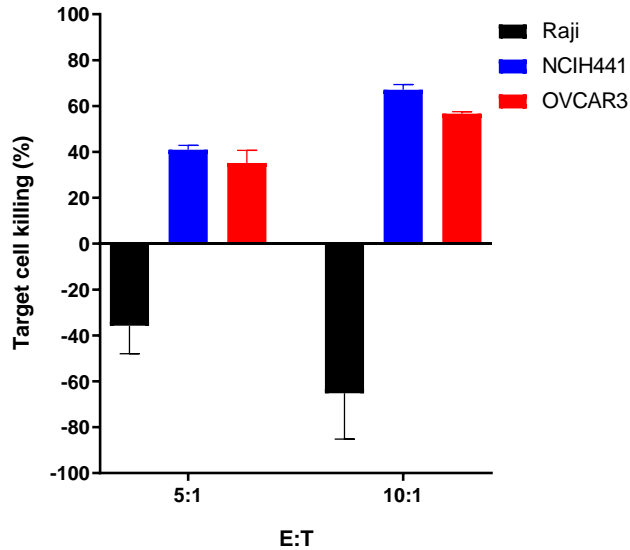
Evaluation of mRNA therapeutics

Case study: *In vitro* efficacy of mRNA-encoded EpCAM-CD3 bispecific antibody

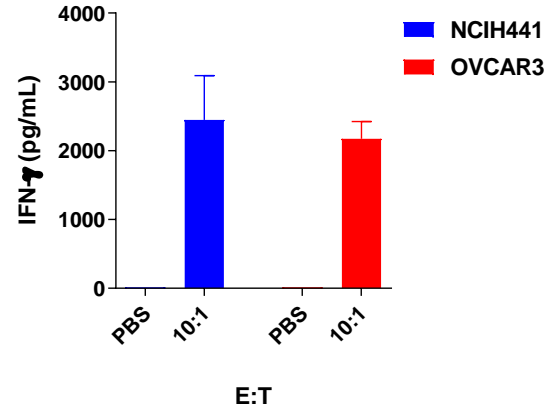
A



B

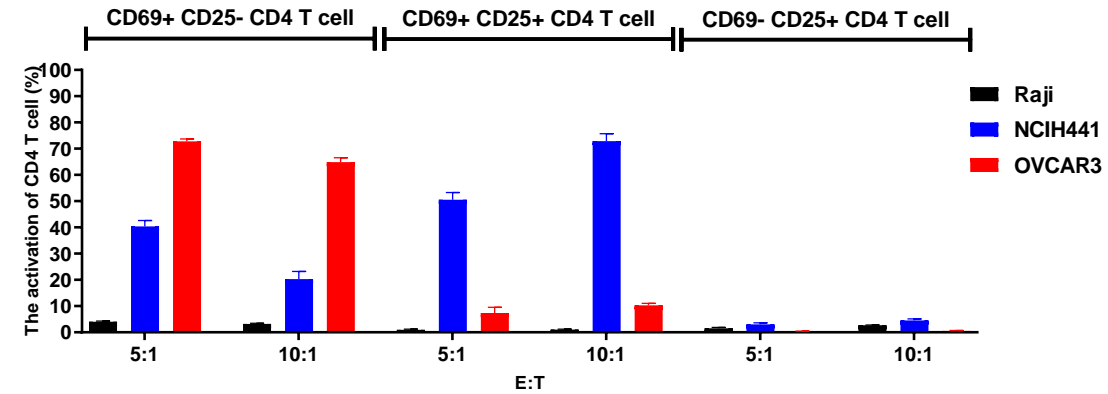


C

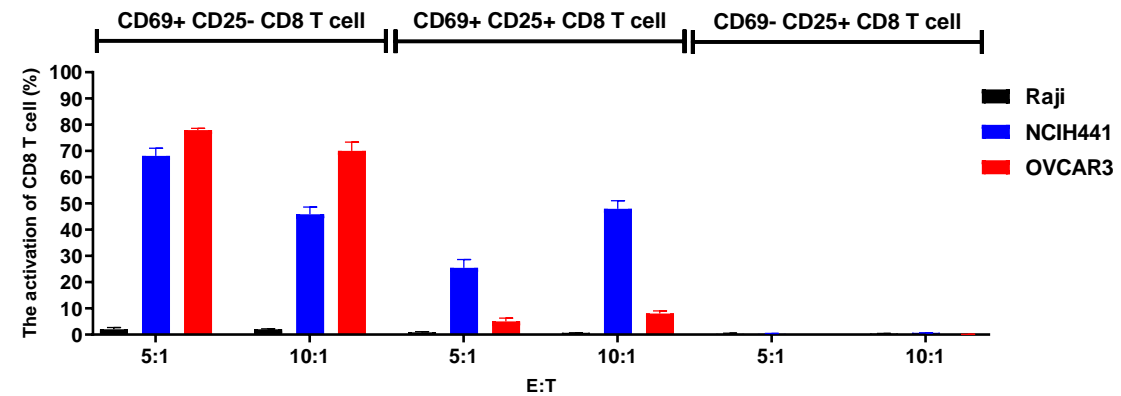


D

The activation of CD4 T cell



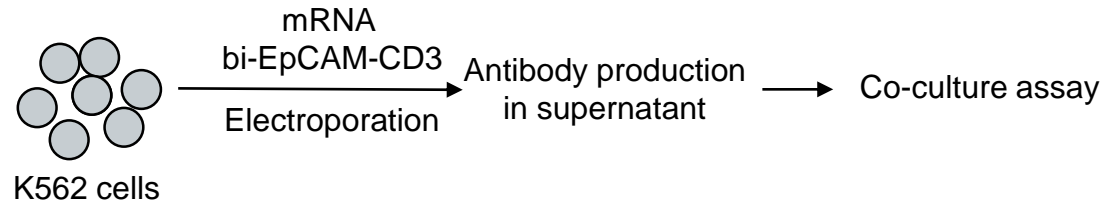
The activation of CD8 T cell



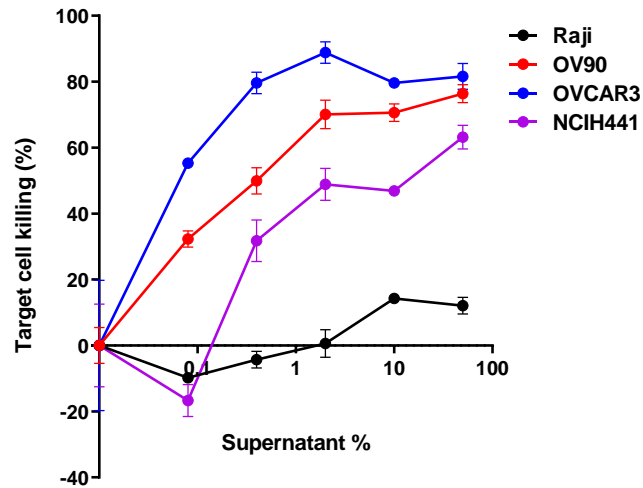
Evaluation of mRNA therapeutics

Case study: *In vitro* efficacy of mRNA-encoded EpCAM-CD3 bispecific antibody

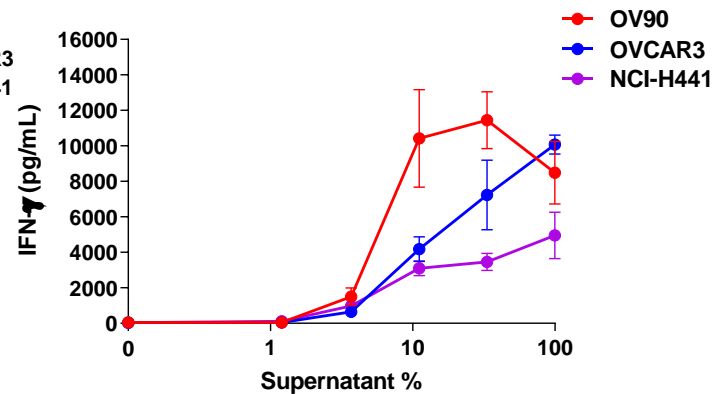
A



B

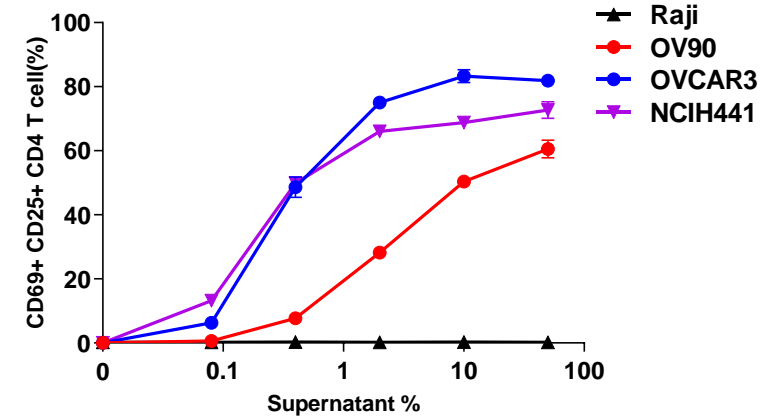


C

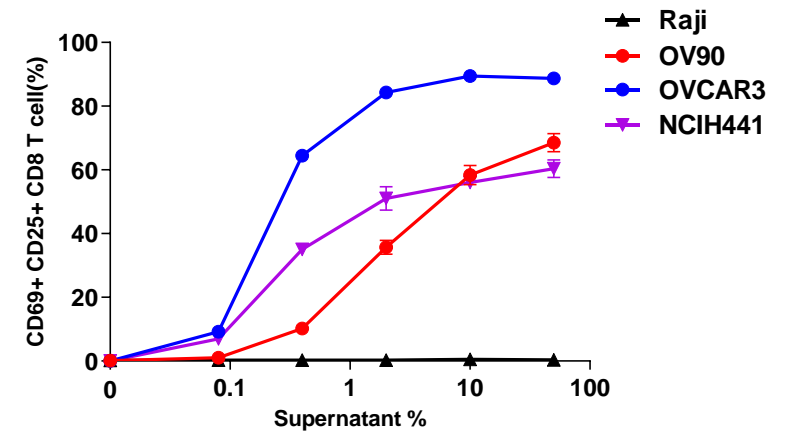


D

The activation of CD4 T cell



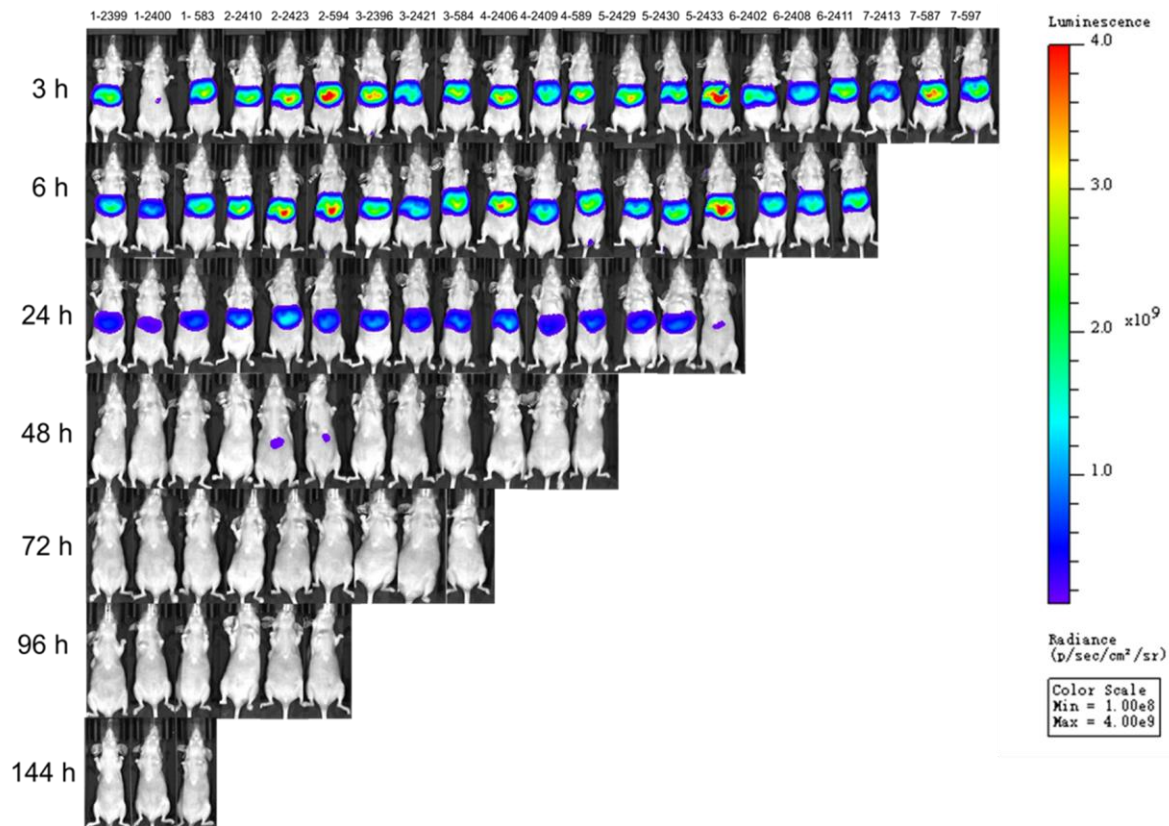
The activation of CD8 T cell



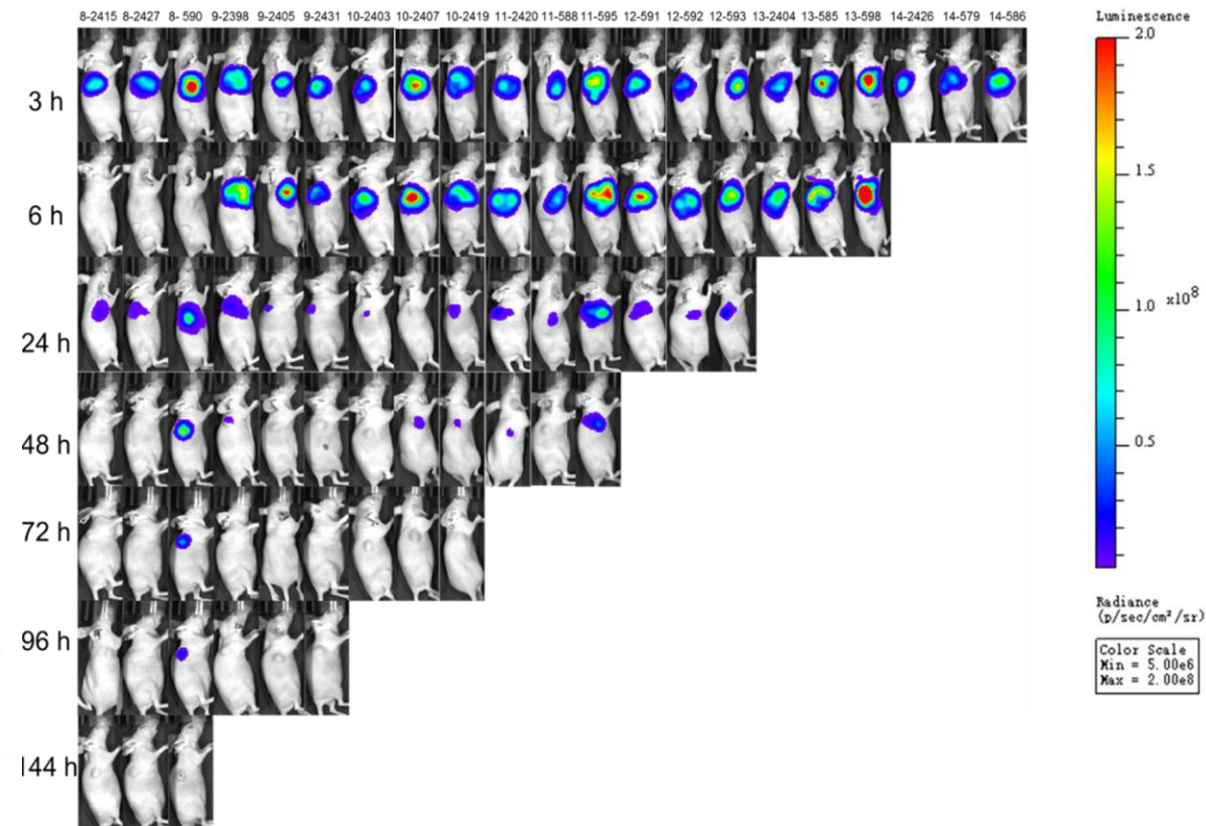
Evaluation of mRNA therapeutics

Case study: *In vivo* biodistribution of mRNA LNP

A Luciferase mRNA LNP in NCI-H441 model
(by IV injection)



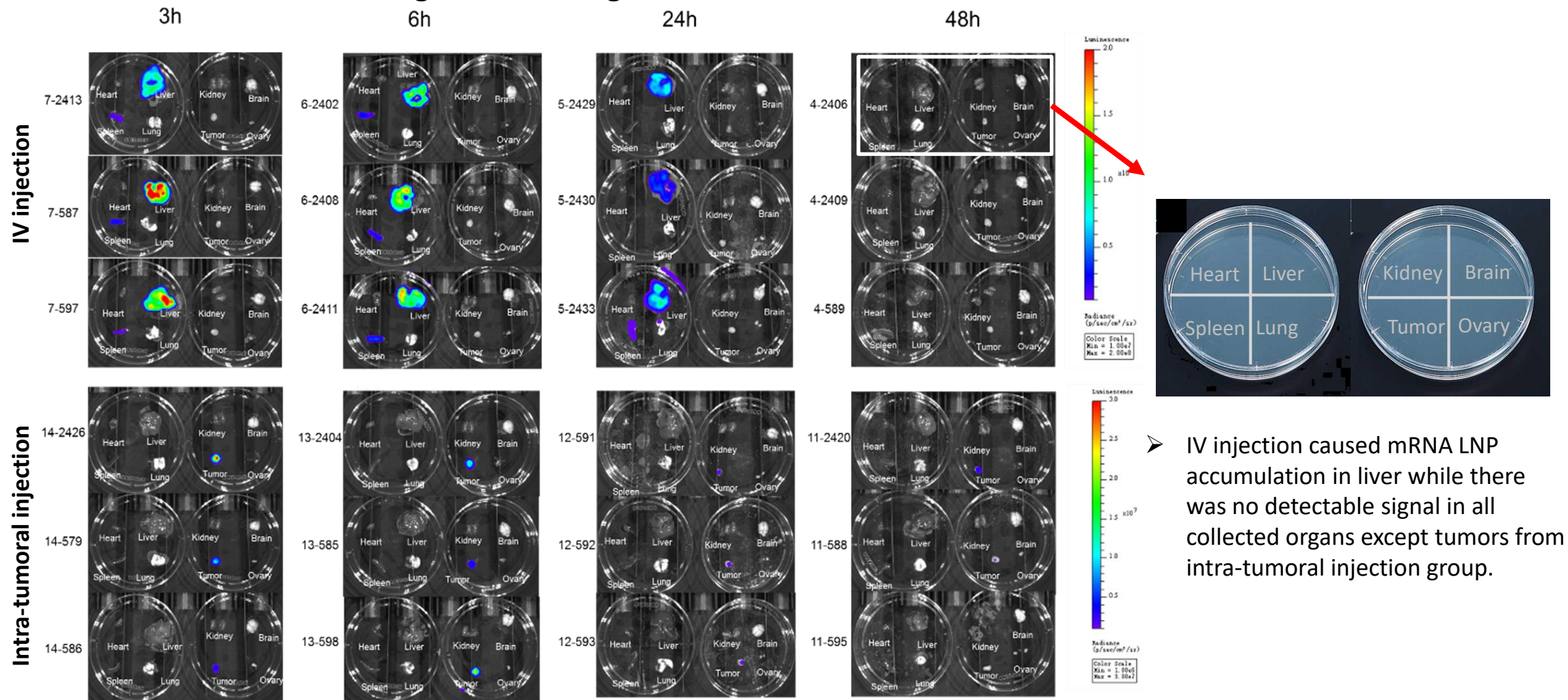
B Luciferase mRNA LNP in NCI-H441 model
(by intra-tumoral injection)



Evaluation of mRNA therapeutics

Case study: *In vivo* biodistribution of mRNA LNP

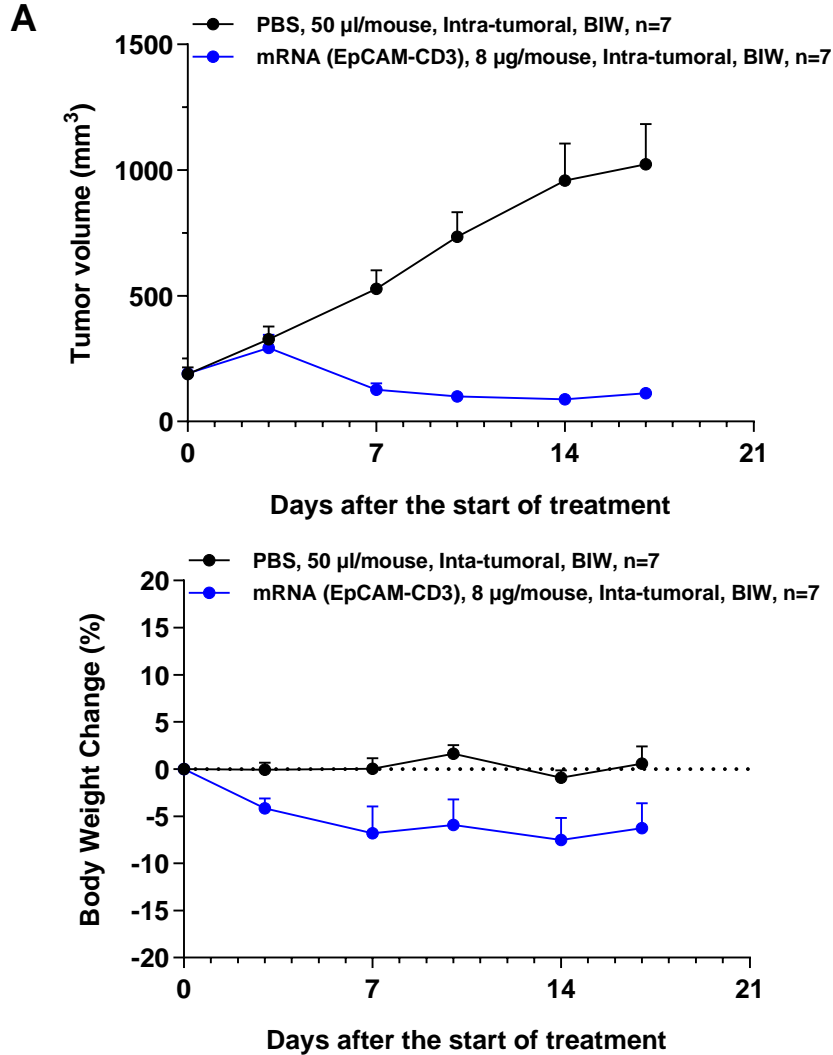
IVIS images of main organs and tumor collected from NCI-H441 model.



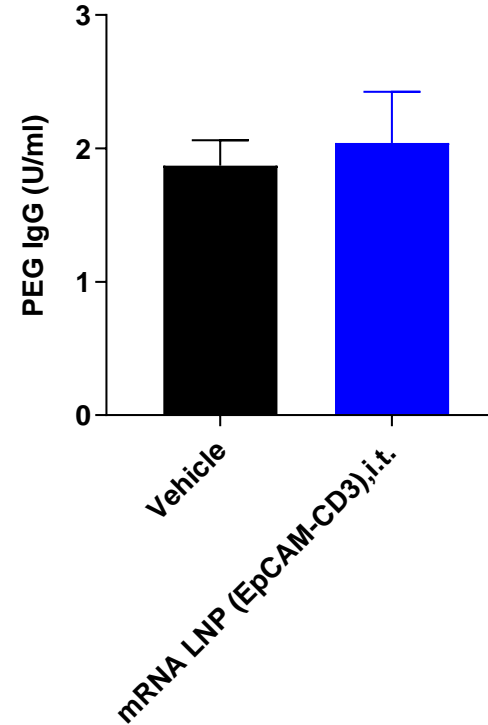
Evaluation of mRNA therapeutics

Case study: *In vivo* efficacy of mRNA-encoded EpCAM-CD3 bispecific antibody in OVCAR3 model

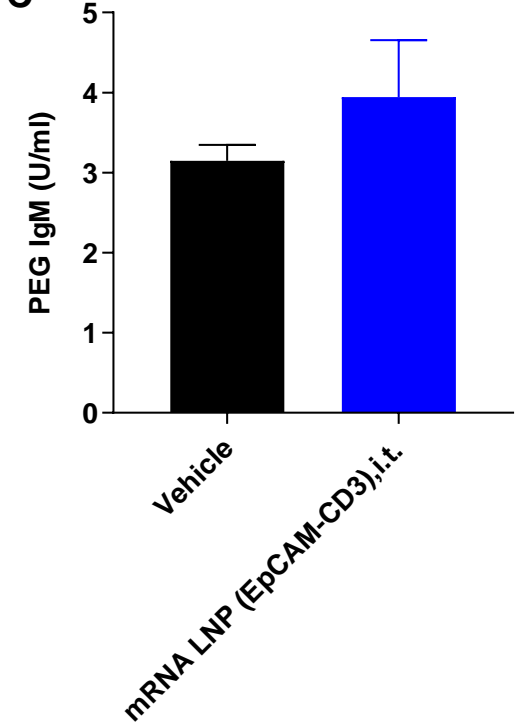
OVCAR3/PBMC humanized model



B

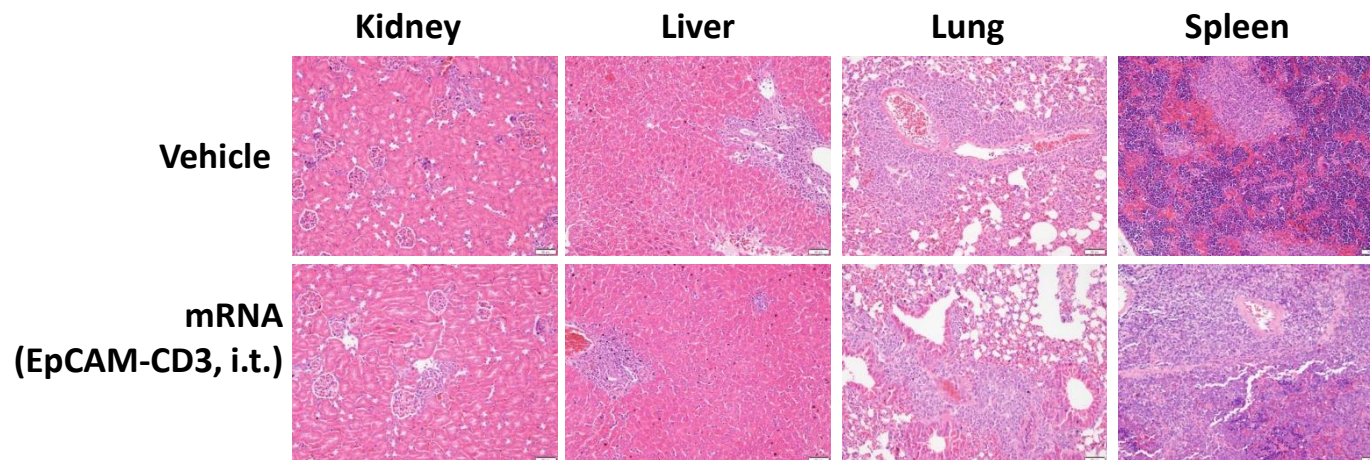
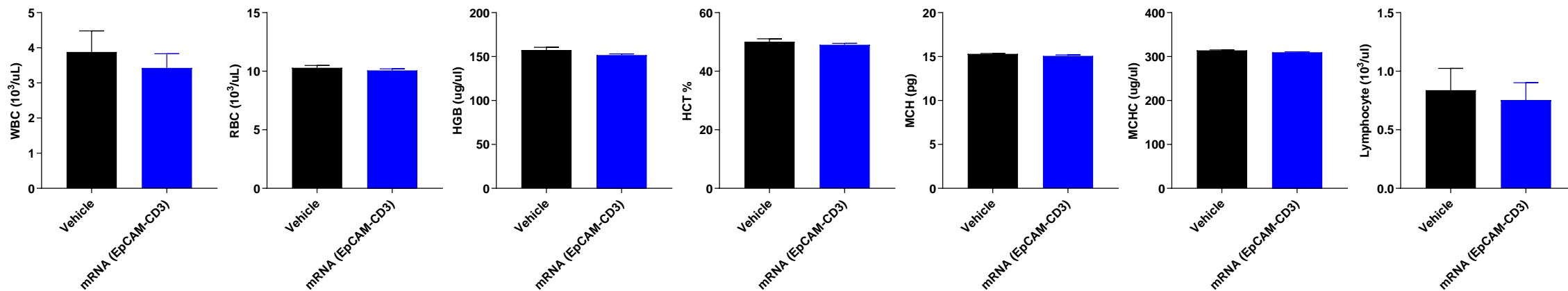


C



Evaluation of mRNA therapeutics

Case study: *In vivo* safety of mRNA-encoded EpCAM-CD3 bispecific antibody in OVCAR3 model

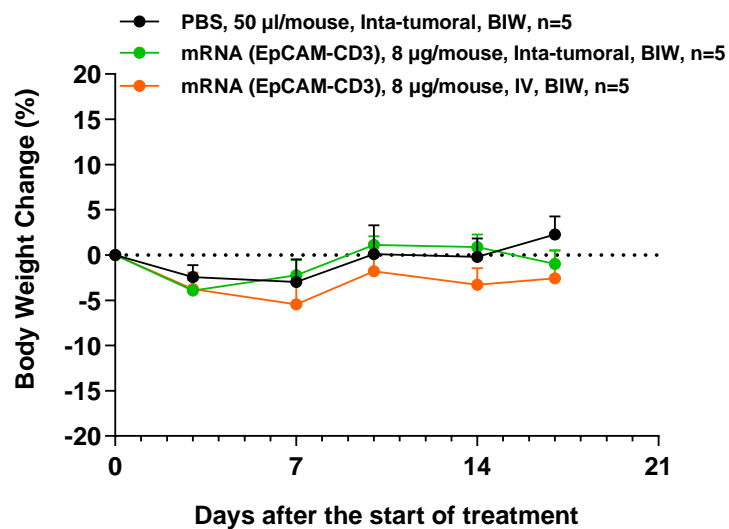
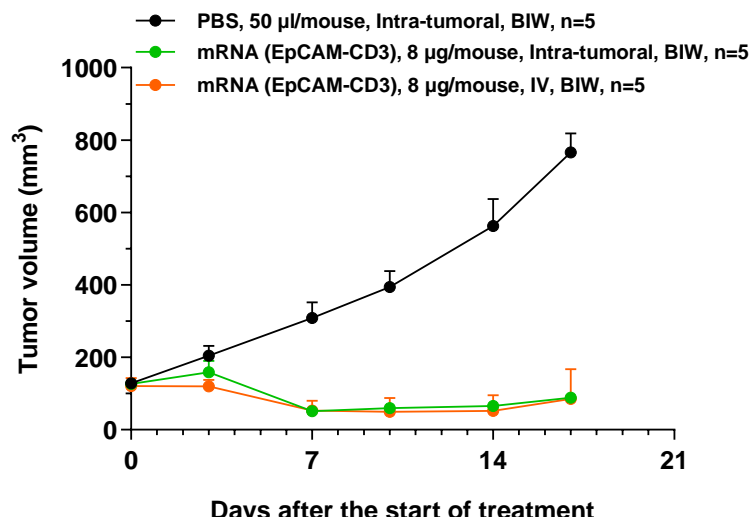


Evaluation of mRNA therapeutics

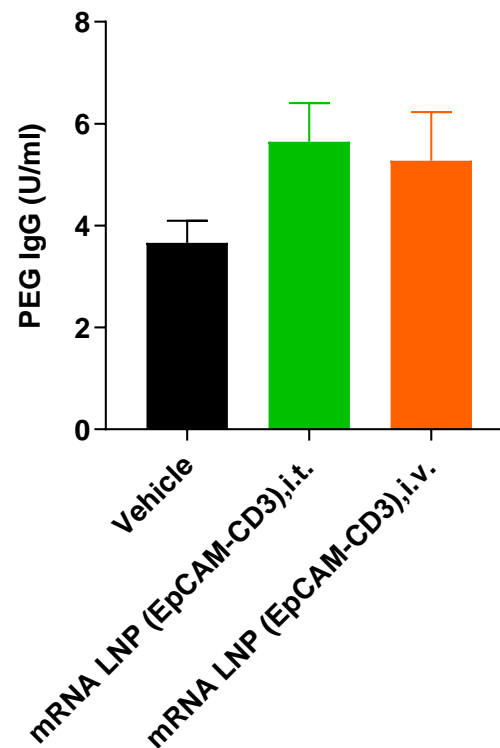
Case study: *In vivo* efficacy of mRNA-encoded EpCAM-CD3 bispecific antibody in NCI-H441 model

NCI-H441/PBMC humanized model

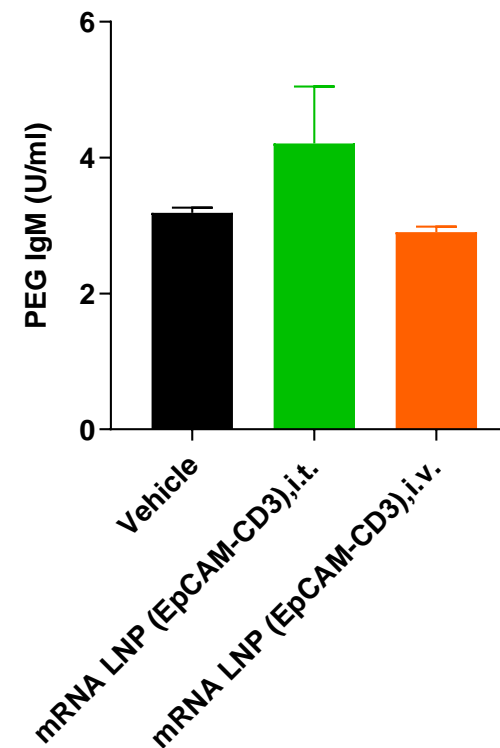
A



B

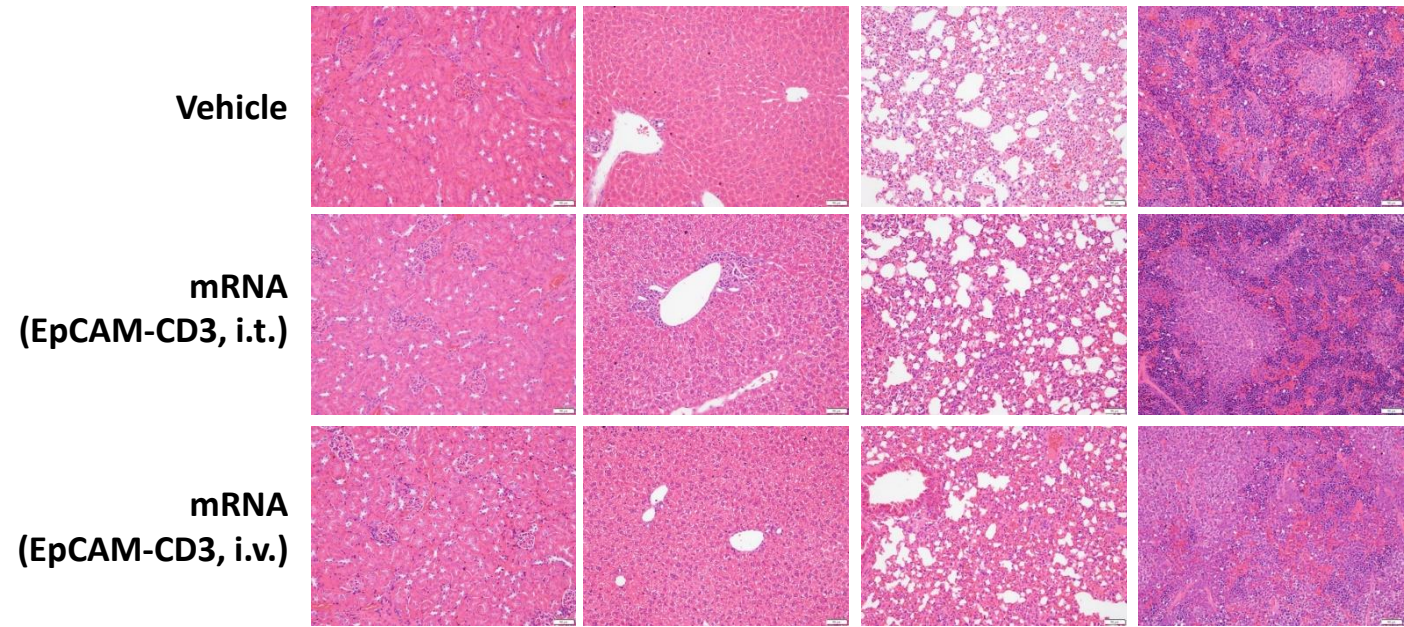
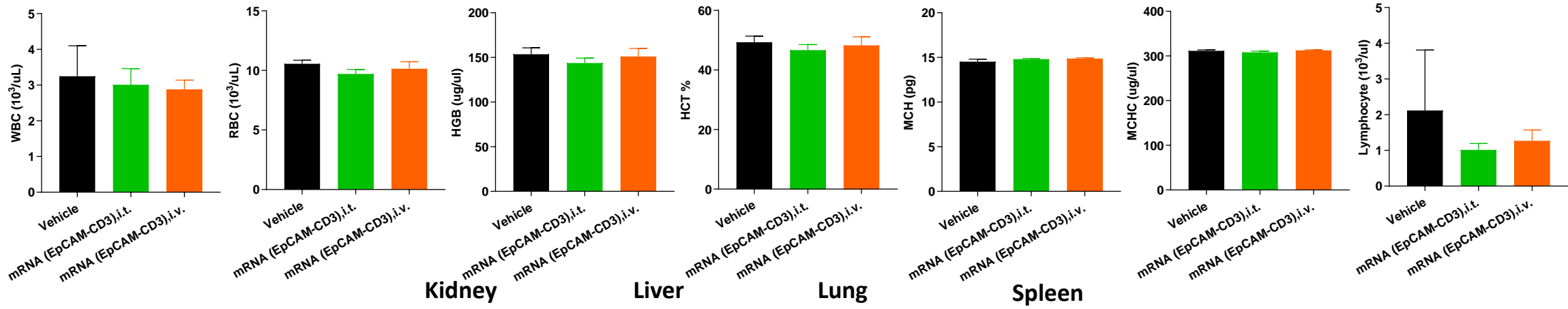


C

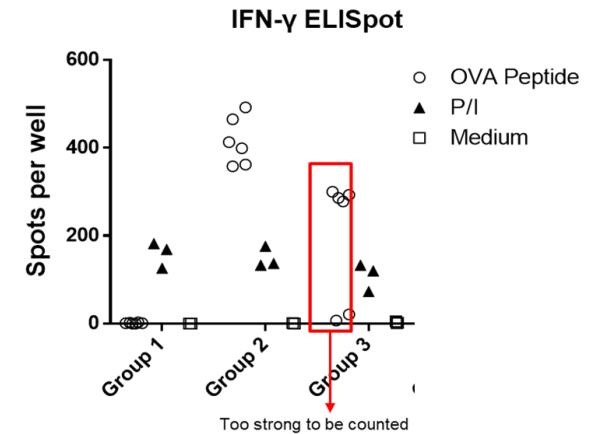
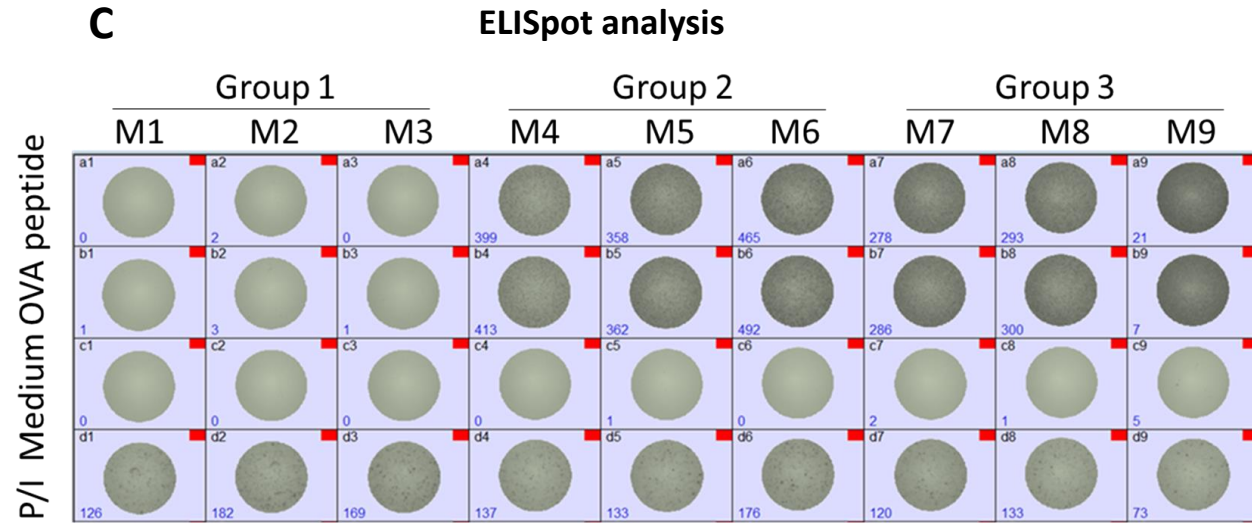
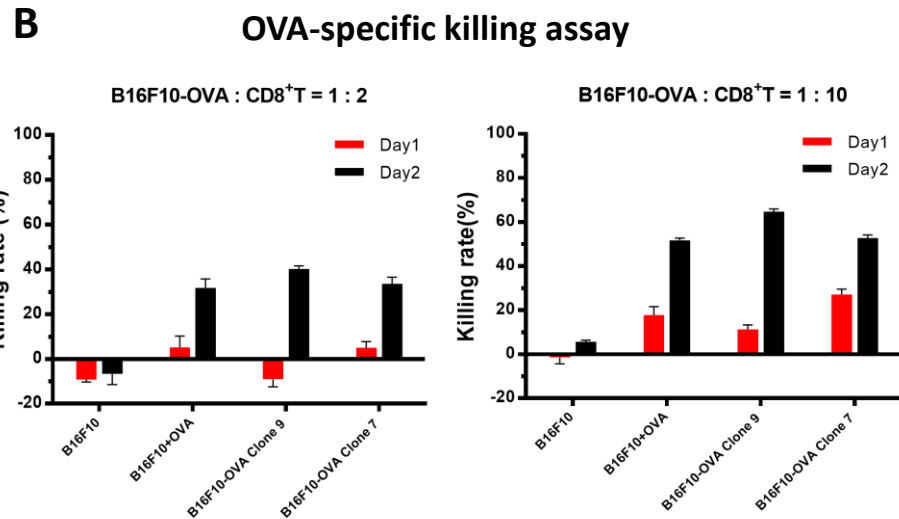
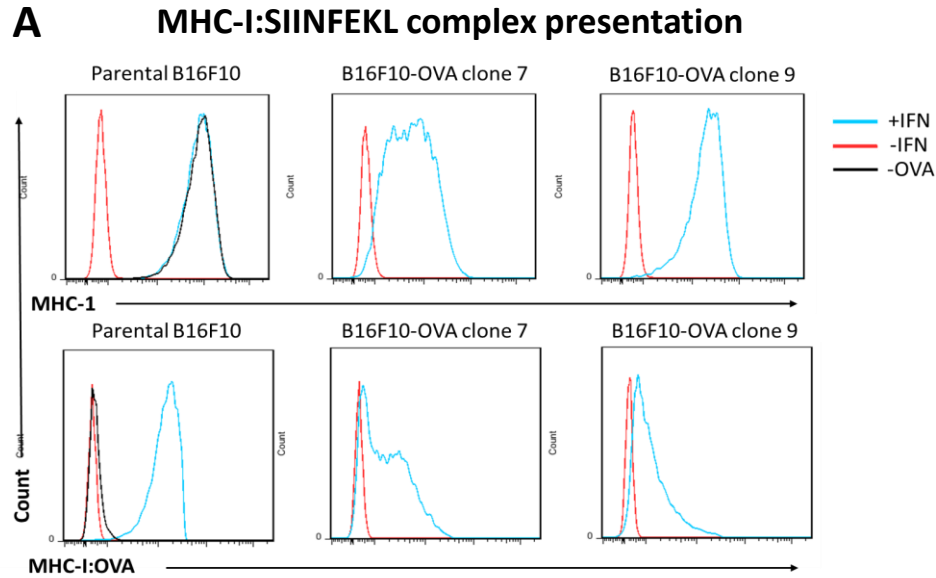


Evaluation of mRNA therapeutics

Case study: *In vivo* safety of mRNA-encoded EpCAM-CD3 bispecific antibody in NCI-H441 model



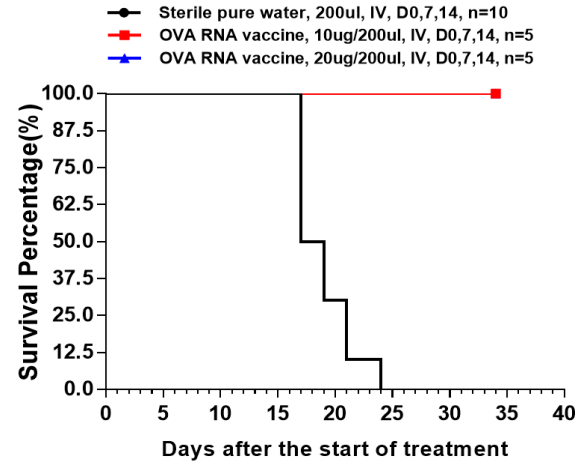
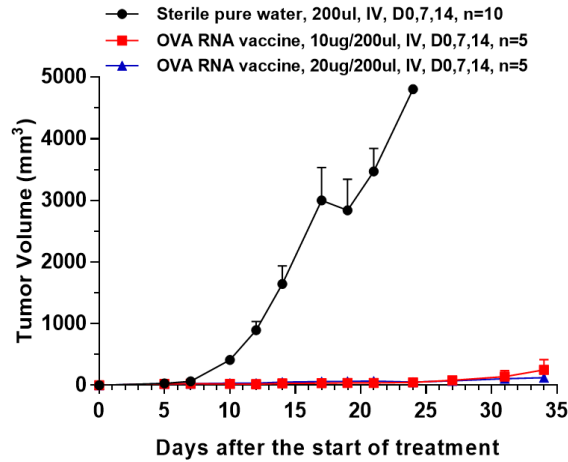
Evaluation of mRNA-encoded OVA vaccine



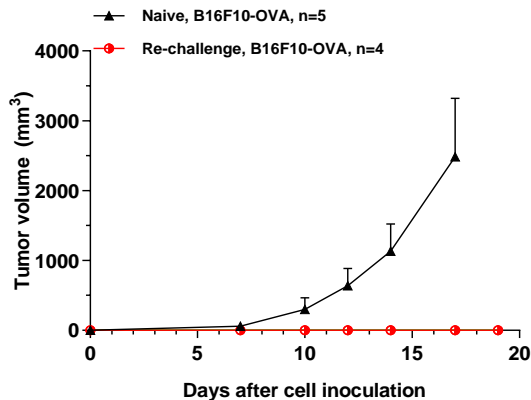
Evaluation of mRNA vaccines

Case study: *In vivo* efficacy and biodistribution of mRNA-encoded OVA vaccine

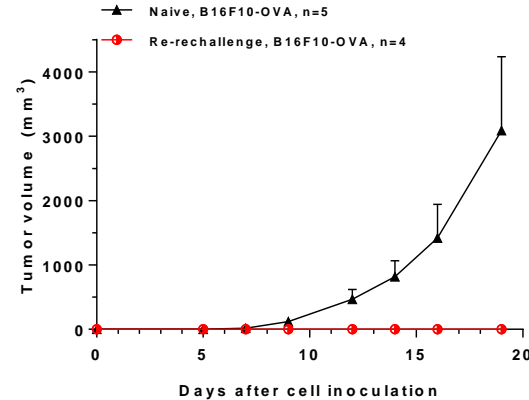
A OVA-specific mRNA in B16F10-OVA model



B 1st round of re-challenge (40 days post vaccination)

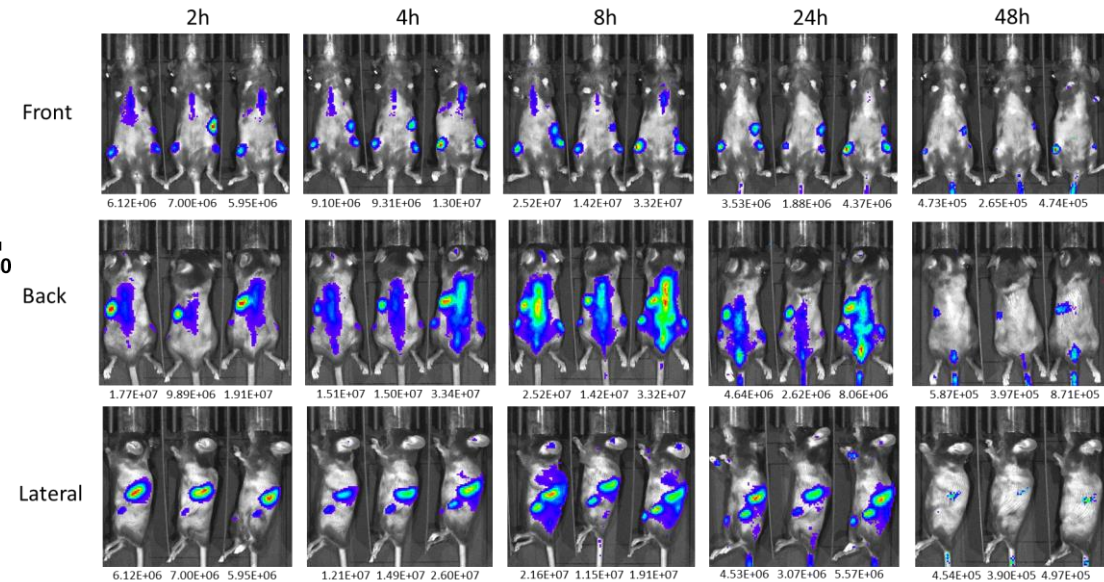


2nd round of re-challenge (100 days post vaccination)



C

In vivo tracking of OVA-specific mRNA





OUR COMMITMENT

Improving Health. Making a Difference.

For questions and requests, please email to OIU-BD-Translation@wuxiapptec.com



<https://onco.wuxiapptec.com>