Self-**A**ssembling and **D**is**A**ssembling (SADA) bispecific antibodies for 2-step Pretargeted Radioimmunotherapy (PRIT)

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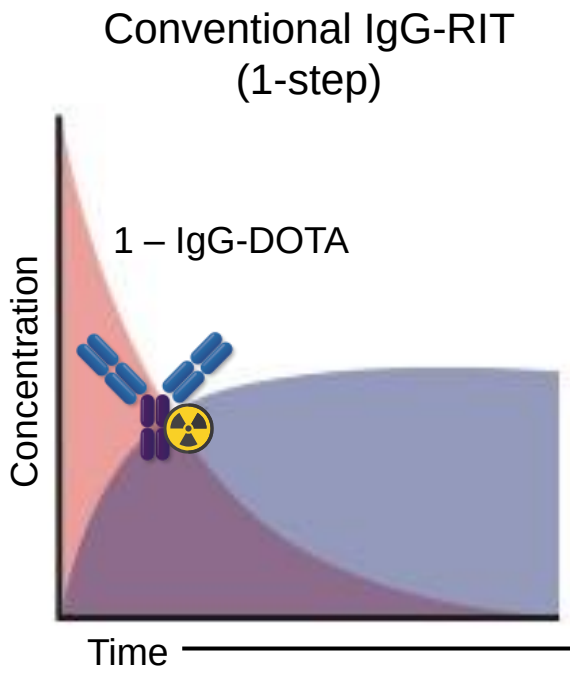
Disclosures

- BS and NKC were named as inventors on US patents (licensed and unlicensed) filed by MSKCC
- SADA Technologies have been licensed to YmAbs Therapeutics
- NKC is an advisory board member for Abpro-Labs and Eureka Therapeutics.
- MSK, NKC, and SML hold financial interest in YmAbs Therapeutics

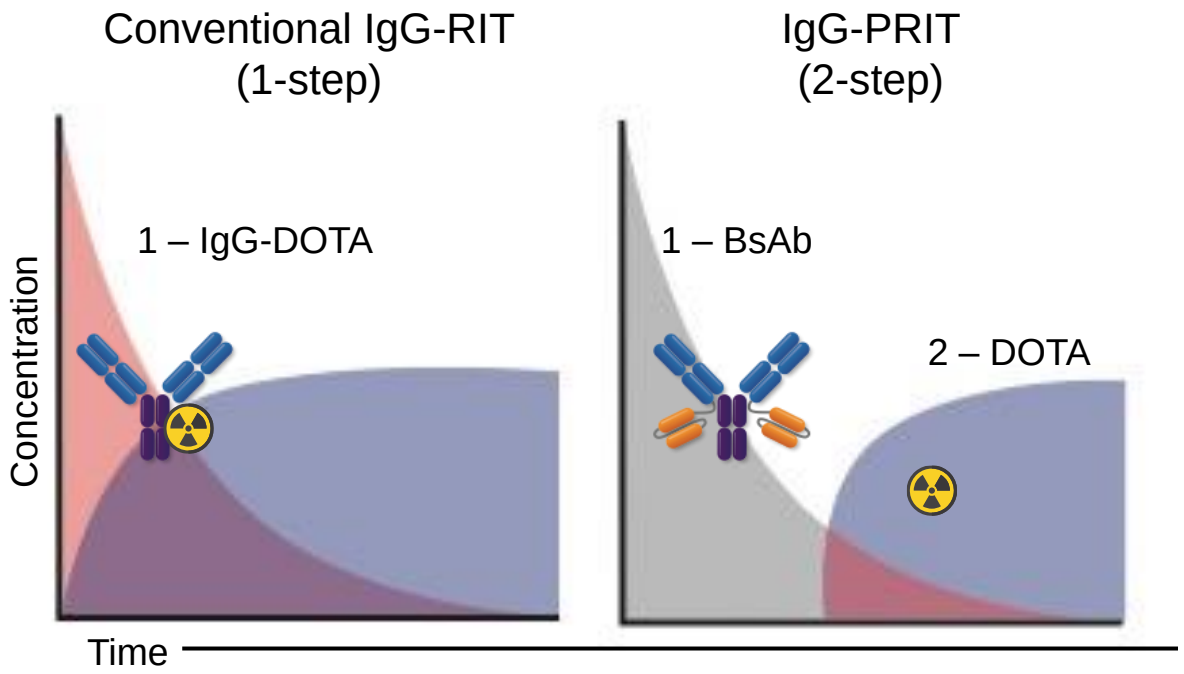
Conventional **R**adio**I**mmuno**T**herapy (RIT) suffers from high levels of unwanted exposure to non-target tissues



Low Tumor:Blood Ratio
High toxicity

Blood exposure (payload)
Tumor uptake (payload)
Antibody clearance

2-step Pretargted RIT (PRIT) improves this, but can still lead to high amounts of radiation to the blood and bone marrow

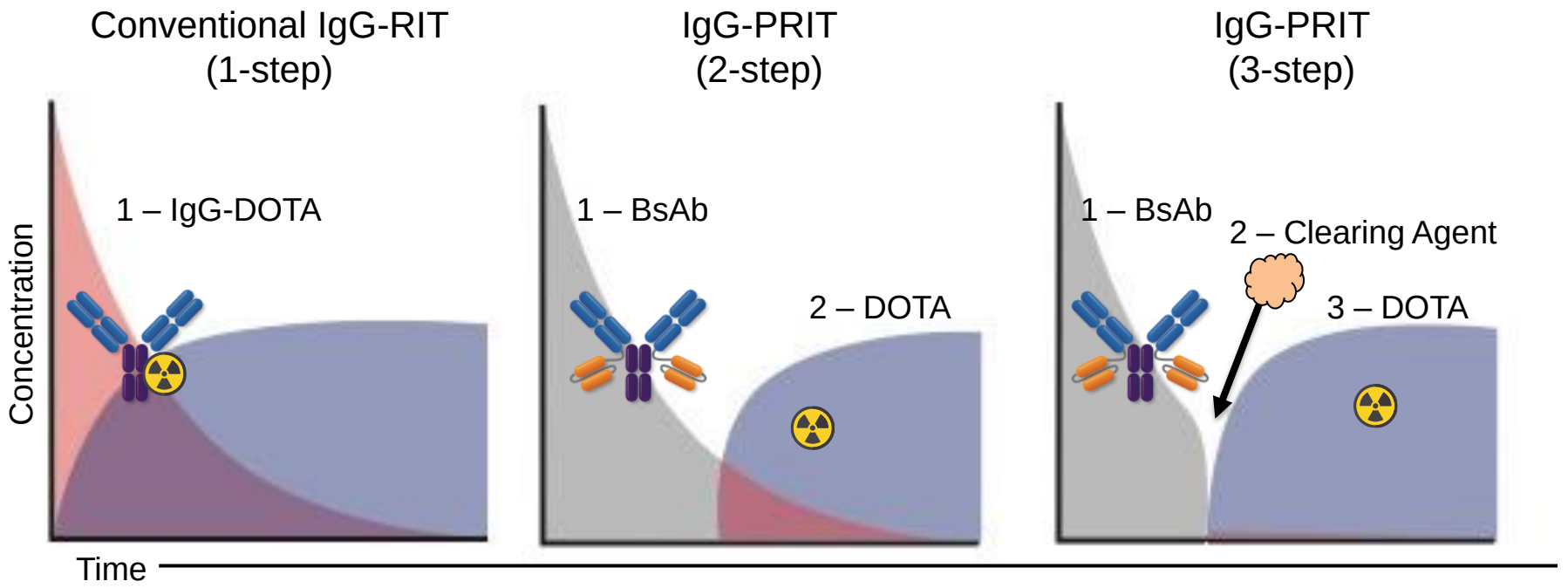


Low Tumor:Blood Ratio
High toxicity

Mid to Hi Tumor:Blood Ratio
Some toxicity

Blood exposure (payload)
Tumor uptake (payload)
Antibody clearance

Adding a clearing agent (3-step PRIT) can mitigate this risk, but also adds complexity to the clinical translation



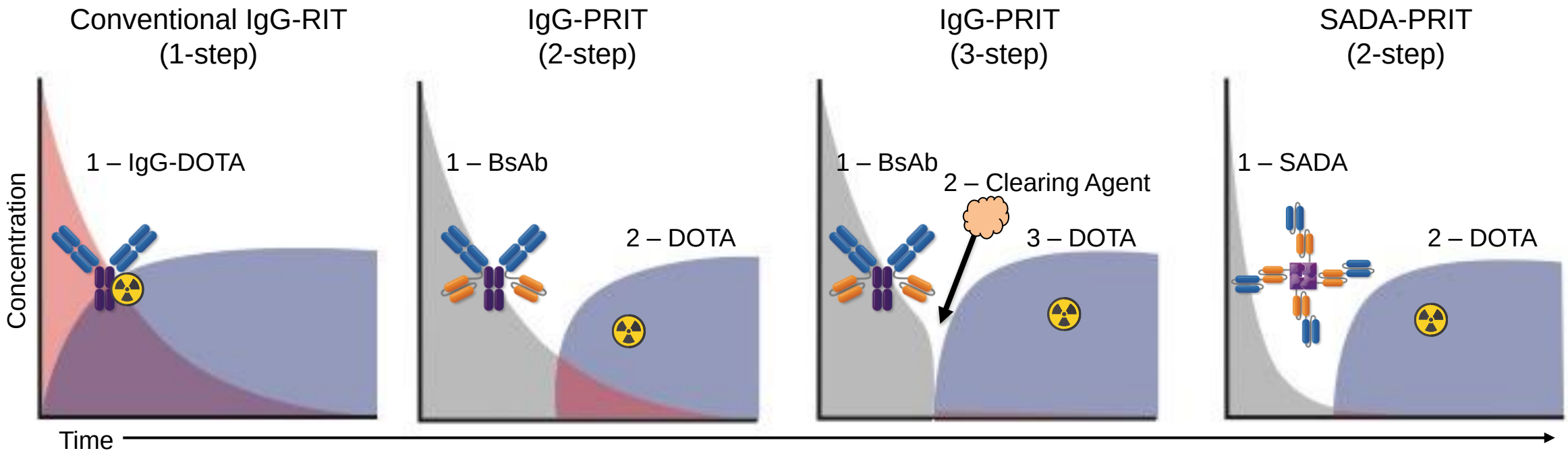
Low Tumor:Blood Ratio
High toxicity

Mid to Hi Tumor:Blood Ratio
Some toxicity

High Tumor:Blood Ratio
Low toxicity
Needs clearing agent

Blood exposure (payload)
Tumor uptake (payload)
Antibody clearance

Ideal 2-step PRIT needs a self-clearing targeting antibody



Low Tumor:Blood Ratio
High toxicity

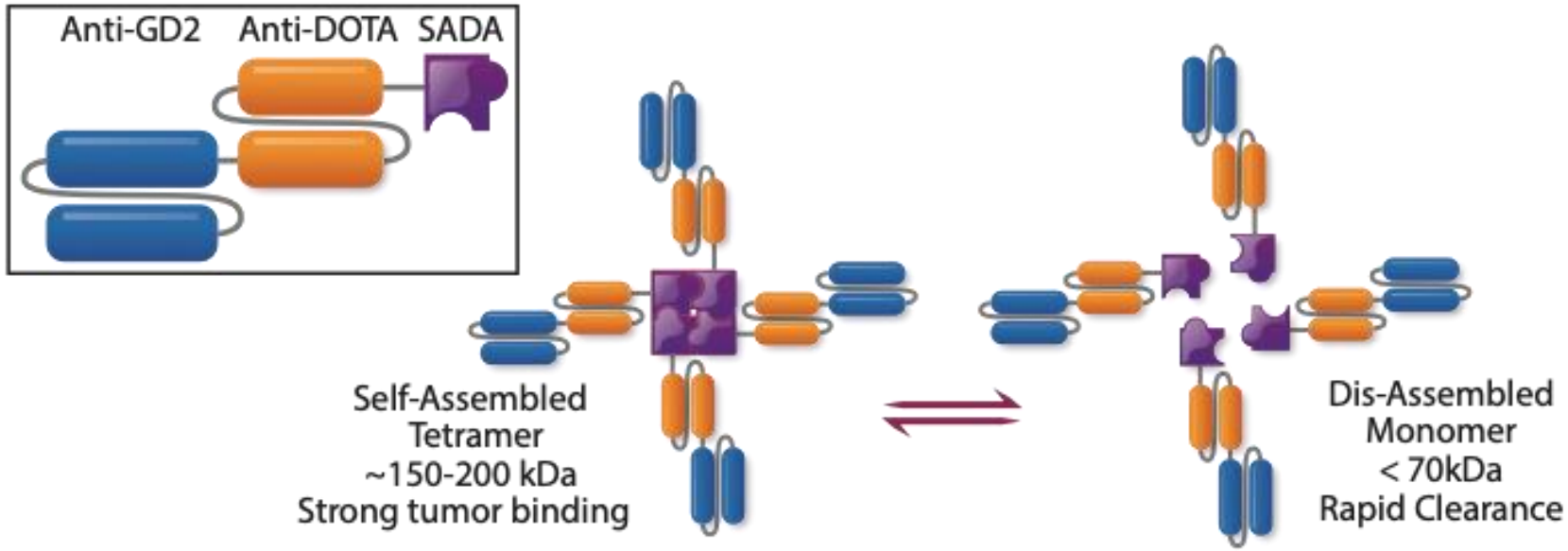
Mid to Hi Tumor:Blood Ratio
Some toxicity

High Tumor:Blood Ratio
Low toxicity
Needs clearing agent

High Tumor:Blood Ratio
Low toxicity
No clearing agent

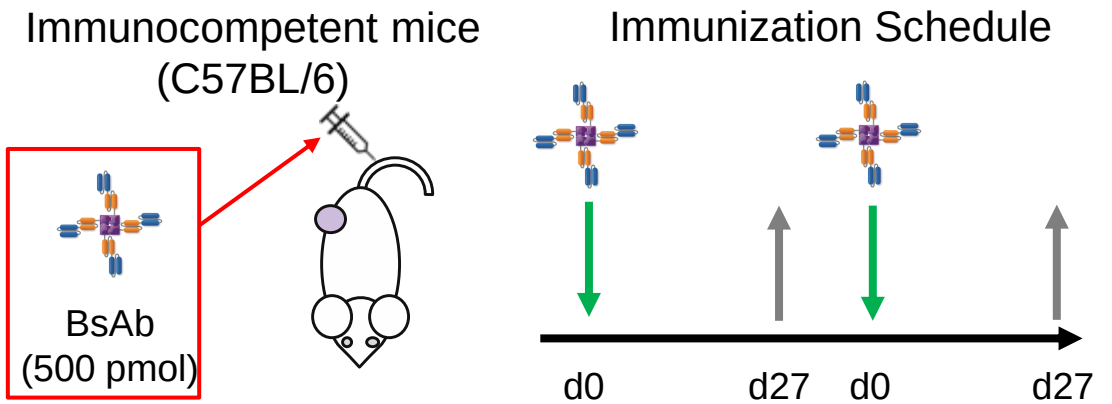
Blood exposure (payload)
Tumor uptake (payload)
Antibody clearance

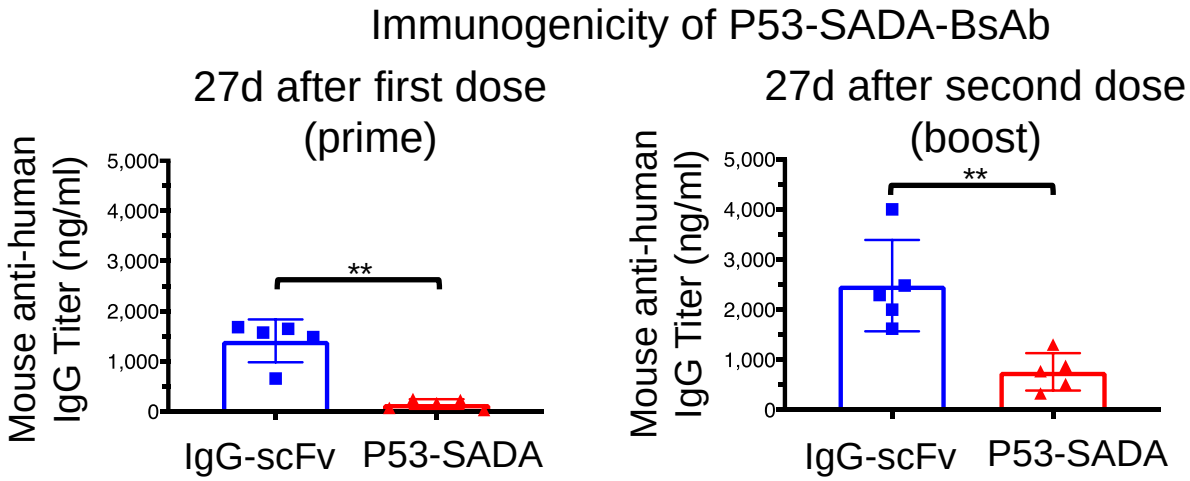
SADA: **S**elf-**A**ssembling and **D**is**A**ssembling domains provide an opportunity to eliminate clearing agent step



BsAb Format	**Terminal Half life**
Tandem scFv (BiTE)	0.45 hour
P53-SADA-BsAb	8 hour
IgG-BsAb	72 hour

Faster clearance kinetics reduces immunogenicity

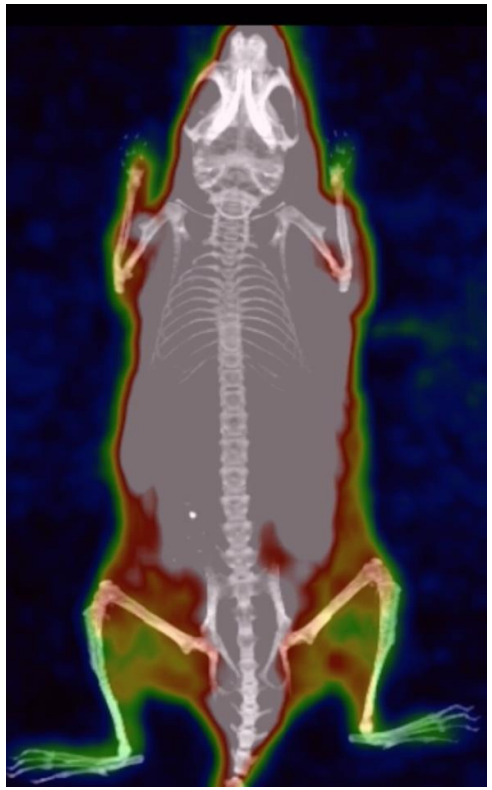




Faster clearance kinetics improves contrast without compromising tumor uptake

PET/CT imaging with DOTA[^{86}Y]
BsAb + DOTA[^{86}Y] 48hours later

IgG-scFv-BsAb
2-step – No CA

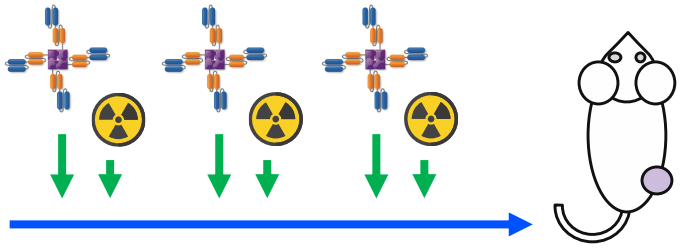


IgG-scFv-BsAb
3-step – with CA

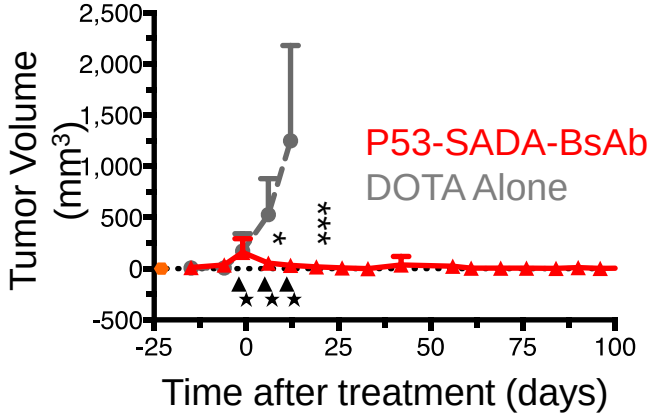
P53-SADA-BsAb
2-step – No CA

2-step SADA PRIT can cure mice implanted with human neuroblastoma xenografts, without renal or hepatic or myelotoxicity

Combined immunodeficiency model
BsAb – 3 x 1.25 nmol
DOTA[^{177}Lu] – 3 x 55.5 MBq

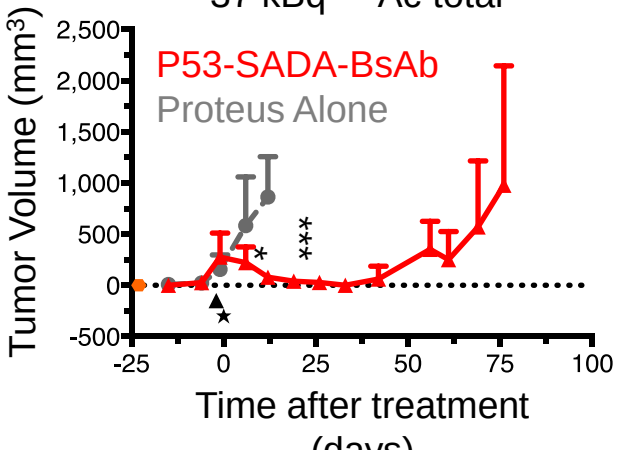


166.5 MBq ^{177}Lu total



Combined immunodeficiency model
BsAb – 1 x 1.25 nmol
Proteus[^{225}Ac] – 1 x 37 kBq

37 kBq ^{225}Ac total

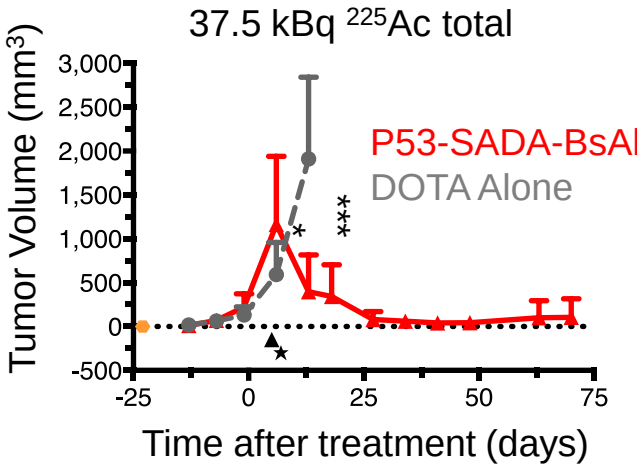


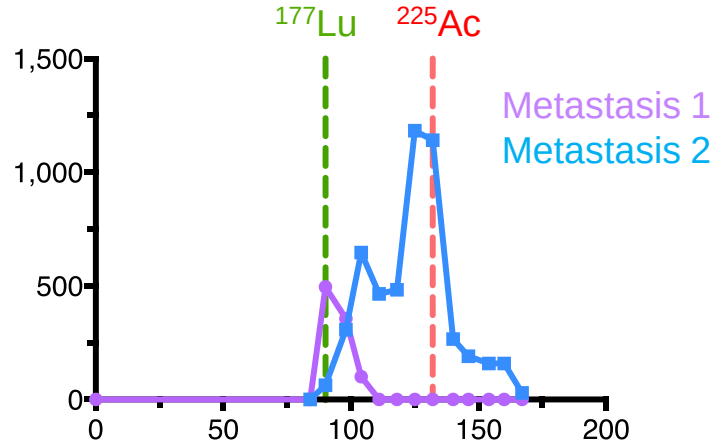
Up to 120 days post treatment

- No damage to bone marrow or blood
  - No myelotoxicity seen during treatment
- No damage to liver
- No damage to kidney (even with ^{225}Ac)
- No brain (GD2^{+}) tissue damage
- Some bladder cystitis (only with ^{177}Lu, not ^{225}Ac)

2-step SADA PRIT can shrink small cell lung-cancer patient derived xenografts (PDX), and metastatic relapses

Combined immunodeficiency model
BsAb – 1 x 1.25 nmol
Proteus[^{225}Ac] – 1 x 37 kBq

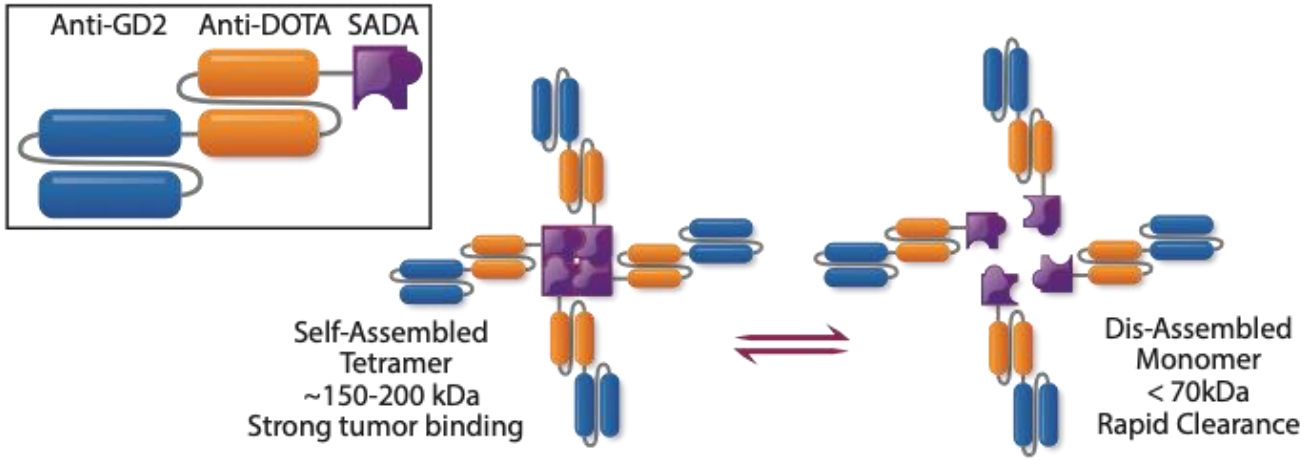




- Large tumors (>1,000 mm3) respond to single dose of ^{225}Ac
- Durability is high, with some relapse
- In a model of metastatic relapse, subcutaneous metastases respond to both ^{177}Lu and ^{225}Ac therapies

Conclusions

- SADA domains allow for rapid clearance of drug, while maintaining high target uptake
  - Less Immunogenicity
  - More contrast
- 2-step payload delivery can be achieved, safely and effectively
  - Tumors shrink while other tissues spared
  - No clearing agent needed
  - No toxicity to bone marrow, kidneys or liver
- SADA system is modular
  - Exemplified with GD2/BnDOTA but other targets and payloads are possible
  - Any DOTA-modified payload
  - Any antigen targeted with an antibody



Acknowledgements

Society of Nuclear Medicine & Molecular Imaging

Funding
- Isabella Santos Foundation
- Jeff Gordon Children's Foundation

Memorial Sloan Kettering Cancer Center
- **Nai-Kong Cheung**
- **Steve Larson**
- **Charles Rudin**
- Michael McDevitt
- Ouathek Ouerfelli

Cheung Lab
- Mahiuddin Ahmed (now YmAbs Therapeutics)
- Hong Xu
- Hong-Fen Guo
- Irene Cheung
- Rebecca Wilen

Larson Lab
- **Sarah Cheal**
- Darren Veach
- Miteshkumar Patel
- Daniela Burnes Vargas

Memorial Sloan Kettering Cancer Center