Therapeutic Antibodies
Next Generation

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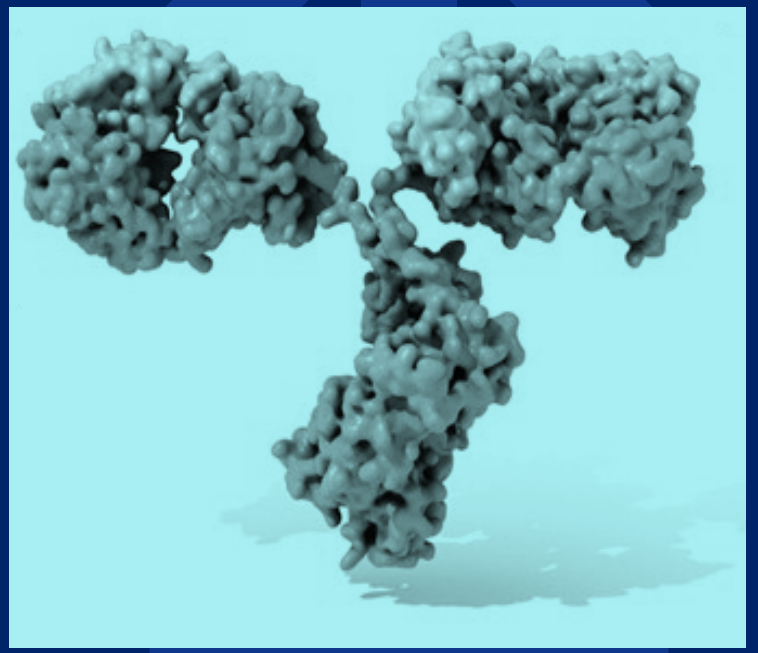
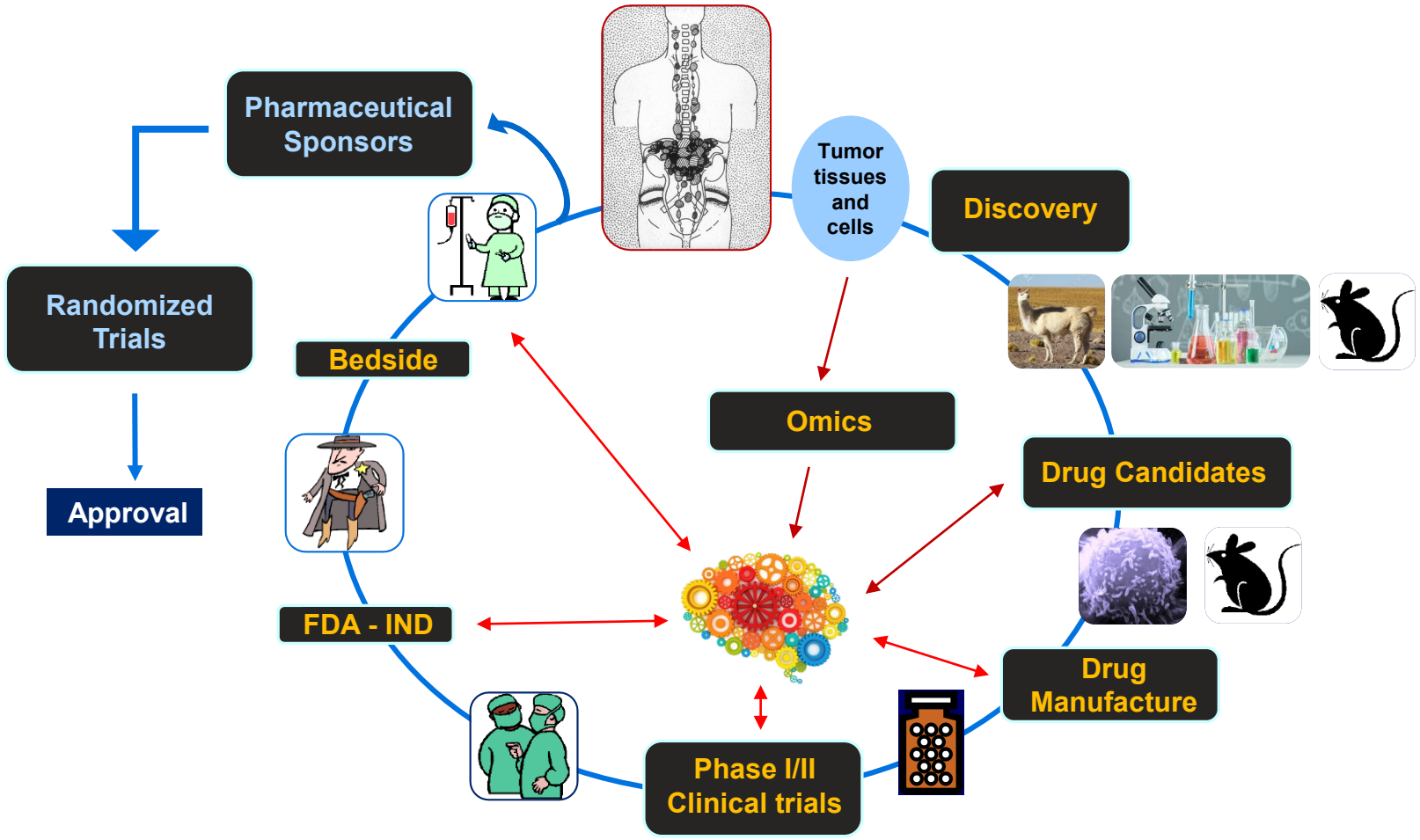
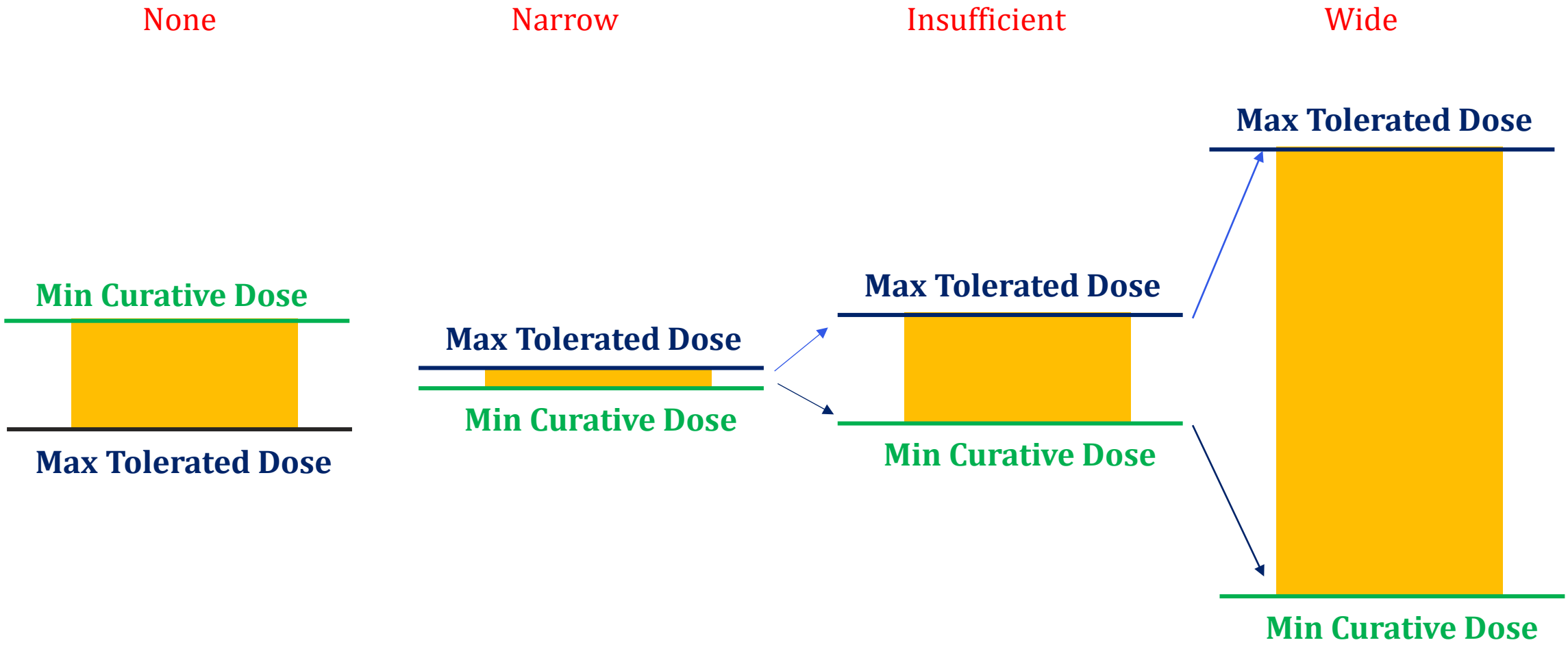


Therapeutics Discovery Translation Cycle



Widening Therapeutic Window is a Must



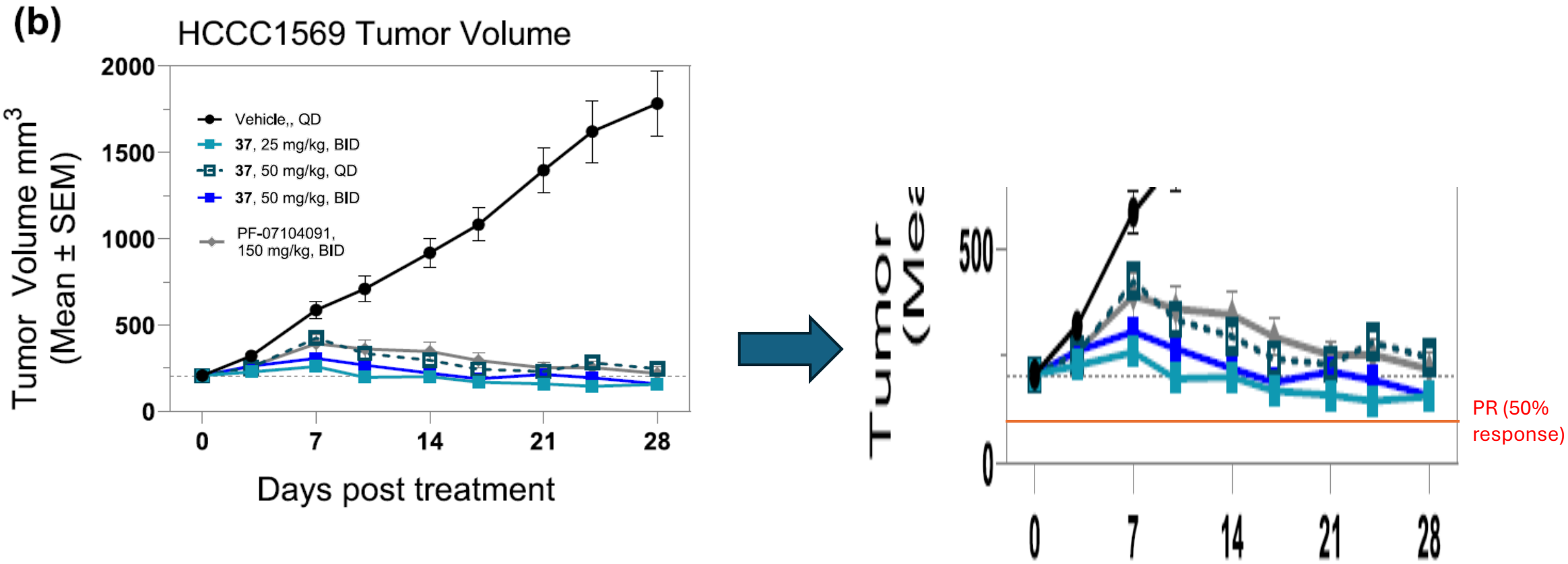
Translation : designing the next cure

Finding the Therapeutic Winner

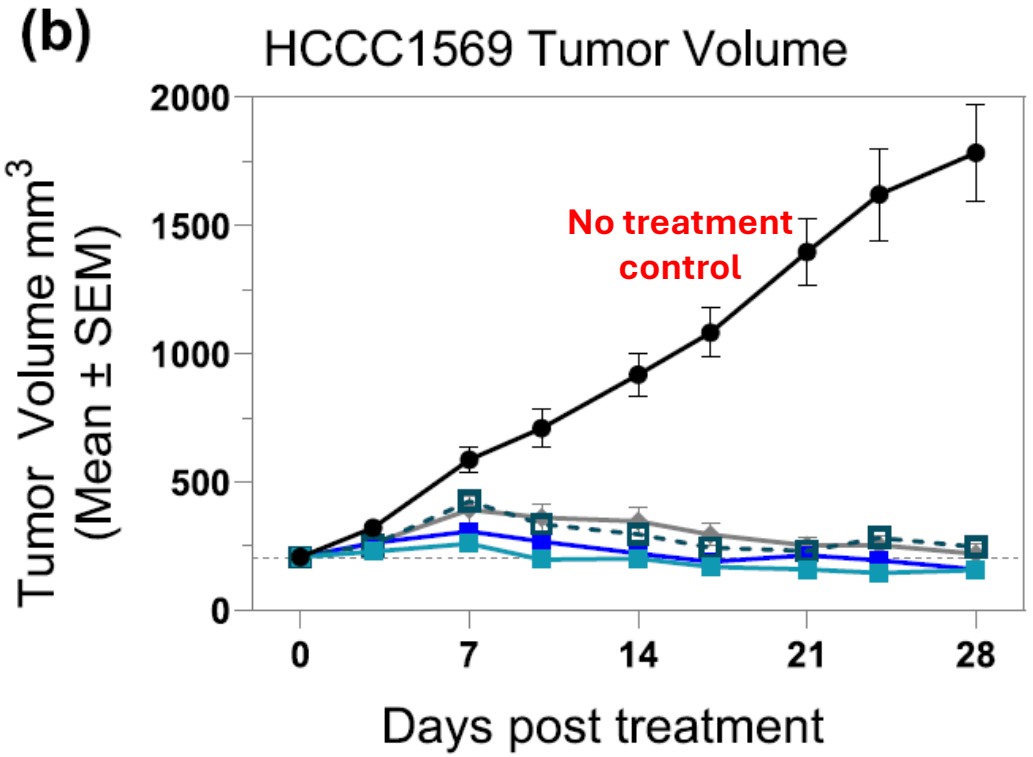
is more than Hypothesis Testing

Mice don’t lie; Humans are biased

Flat tumor growth maybe a warning sign



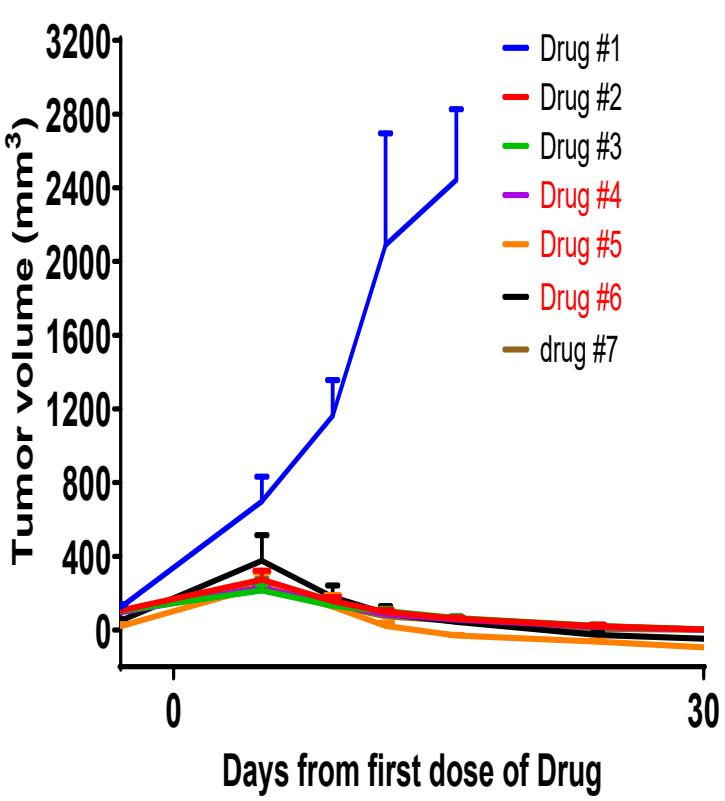
“No Treatment” (Vehicle) is not the appropriate Control

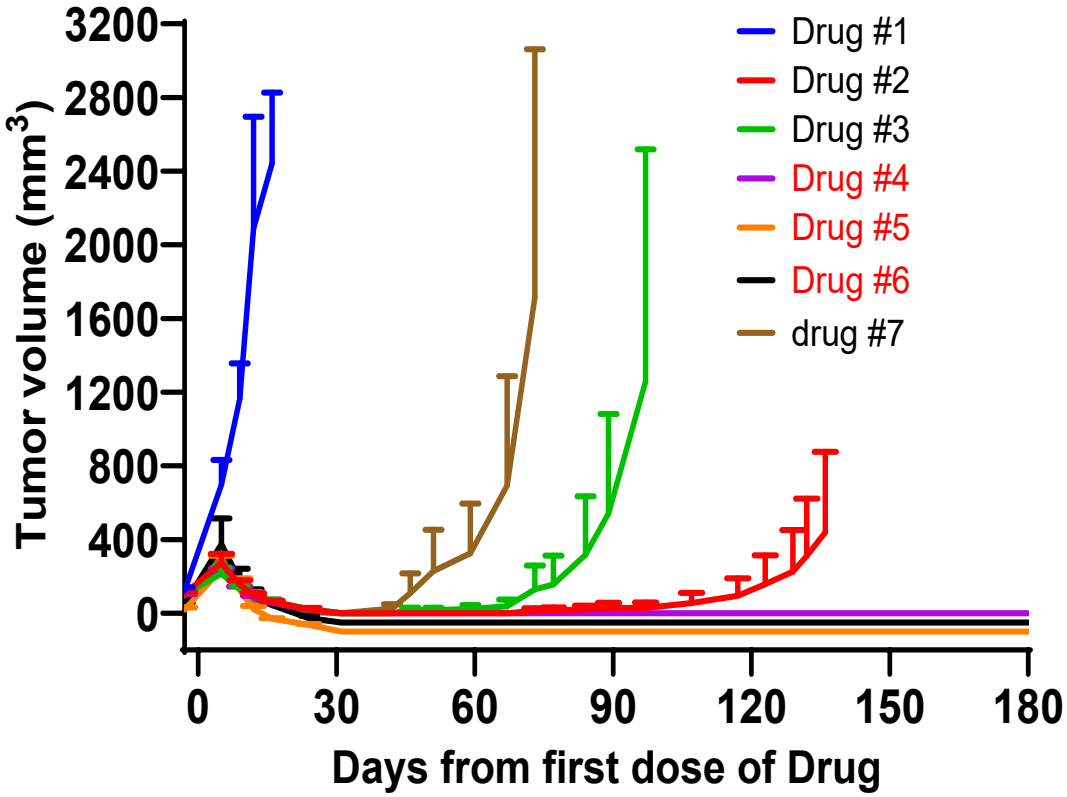


Appropriate Control:

Standard of Care (Cancer type specific, risk group specific)

Short duration of response is not cure



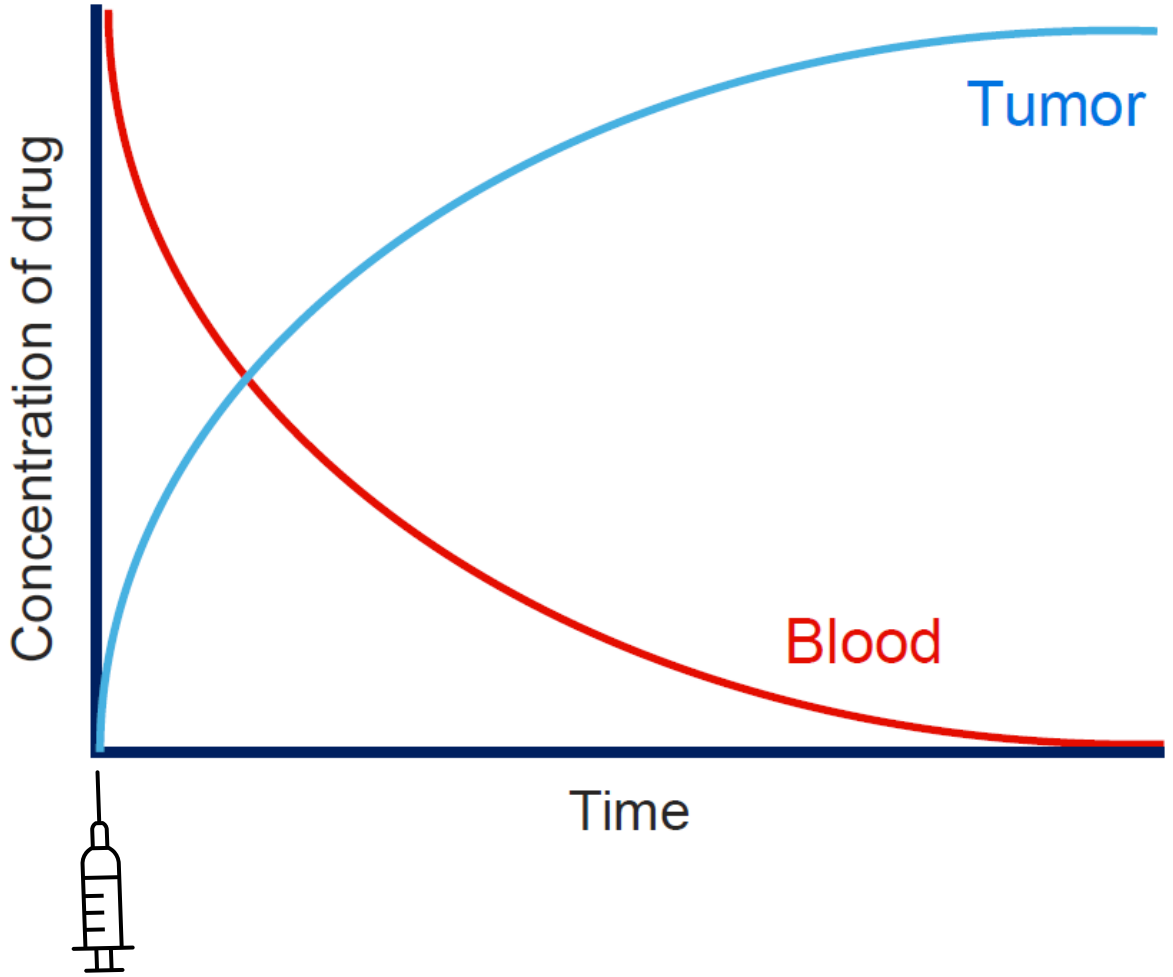


Median PFS or OS:

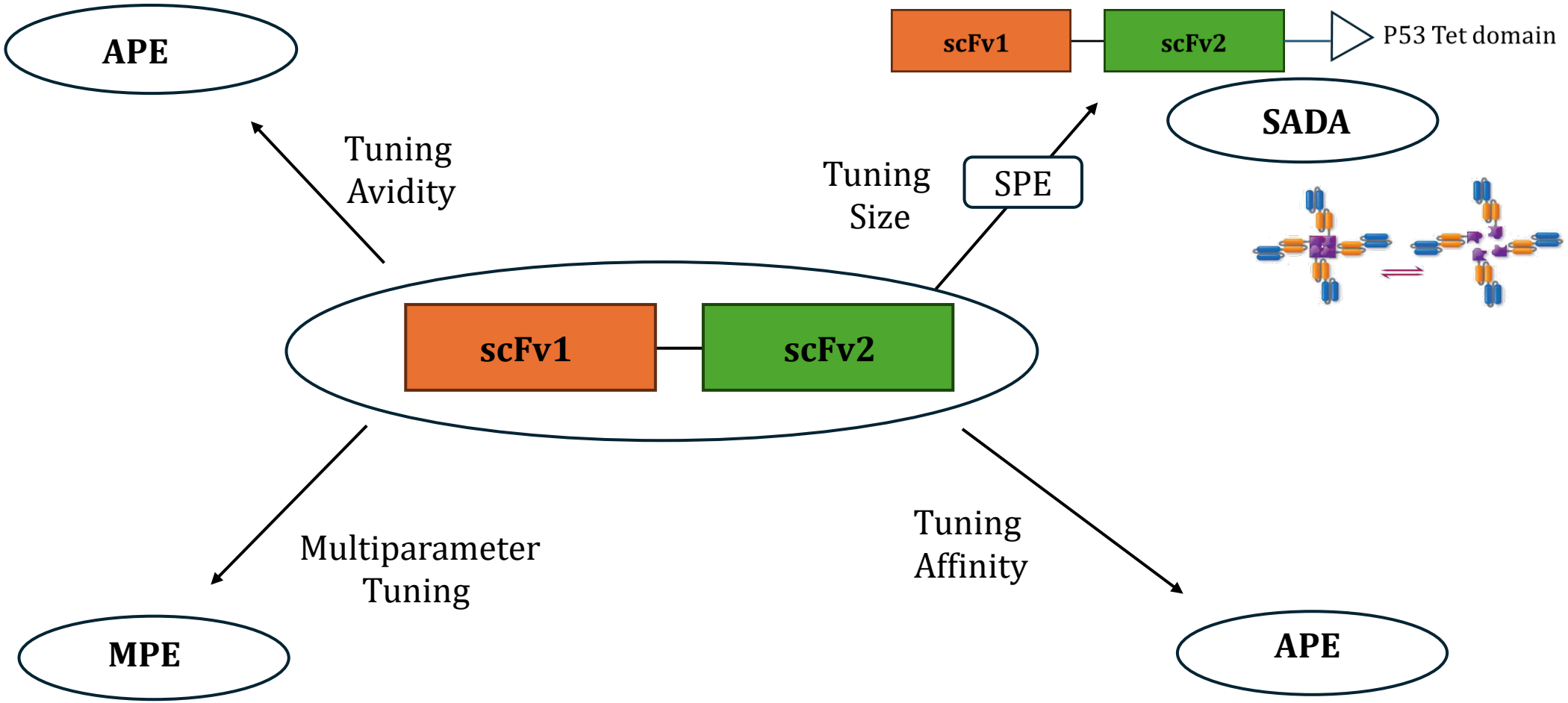
Significance (p value) is only half of the story

Effect Size is just as important

PK of Antibody Delivery Systems

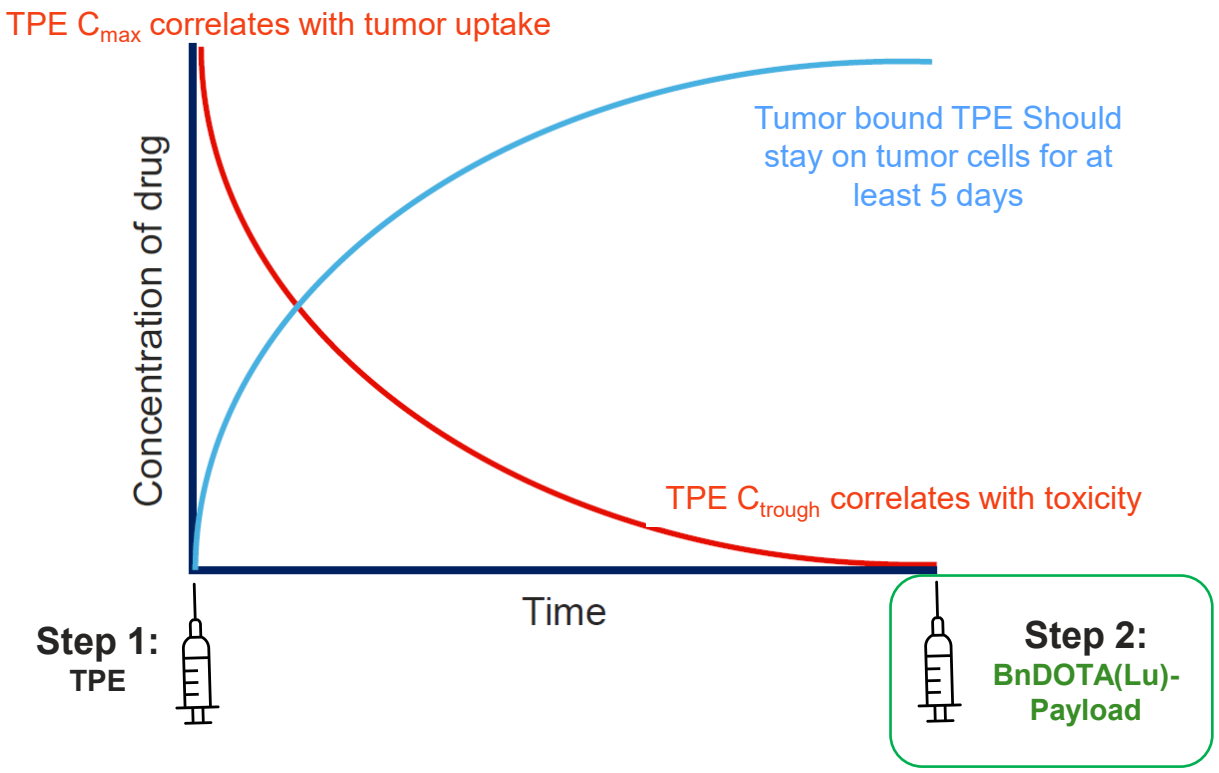


TPE (Targeted Payload Engager) Multispecific Antibody



2-Step Pretargeted Radioimmunotherapy

STEP#1 : **TPE antibody**

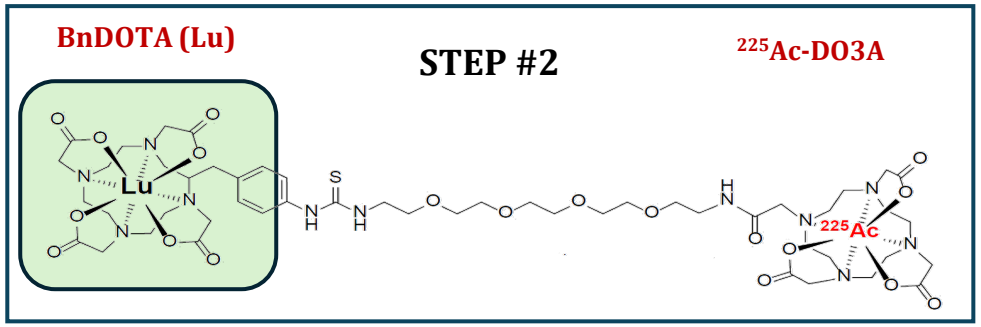


STEP#2 : **BnDOTA(Lu) - Payload**

DO3A
- ^{177}Lu
- ^{225}Ac
- ^{161}Tb
- ^{89}Zr
- ^{86}Y

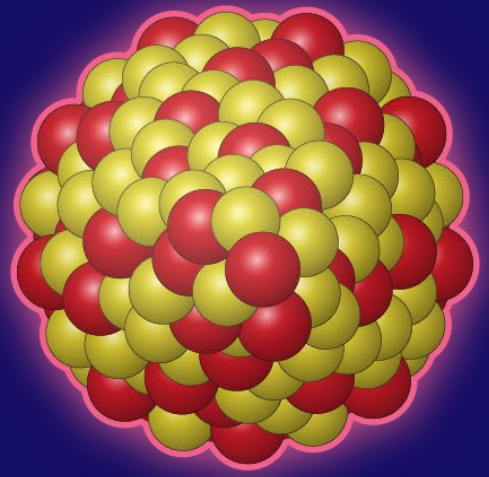
TCMC
- ^{212}Pb
- ^{203}Pb

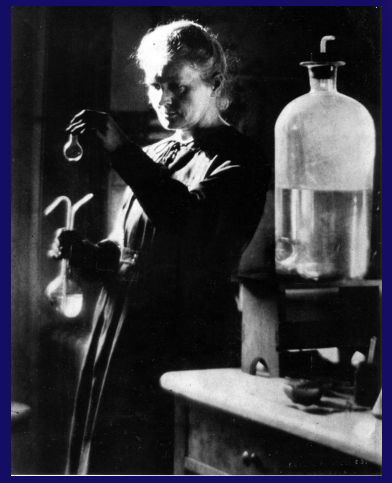
DOTAGA
- ^{67}Cu
- ^{64}Cu

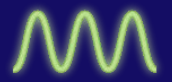


With wide Therapeutic Window: Let's try the unthinkable

Lutetium 177
Terbium 161
Actinium 225
Lead 212







Gamma (photon)
No charge
High penetration of tissues
Low ionization potential
No mass

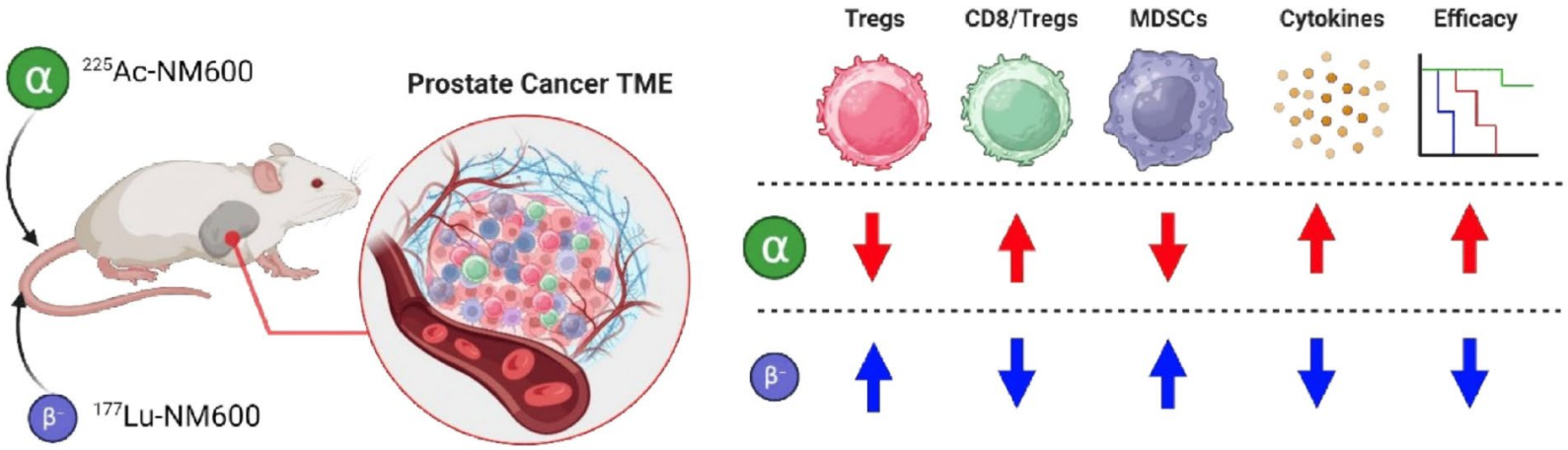
Beta (electron)
Charge of -1
Penetrates 2-3 mm in tissue
Low ionization potential
Rest mass energy **0.5 MeV**

Proton (1p particle)
Charge of +1
Penetrates tissue
Higher ionization potential
Rest mass energy **938 MeV**

Alpha (2p + 2n particle)
Charge of +2
Penetrates 0.05-0.1mm in tissue
Highest ionization potential
Rest mass energy **3800 MeV**

Alpha therapy over beta therapy

- Superior cytotoxicity: Alpha particle 8000x size of beta particle, 500x more cytotoxic
- Higher LET delivers dense nonreparable double strain DNA breaks
- Not reliant on oxidative intermediates, ignores hypoxia
- Reduces immunosuppressive cells (Treg, MDSC)
- Promotes immunogenic cell death – Strengthens Ascopal effects

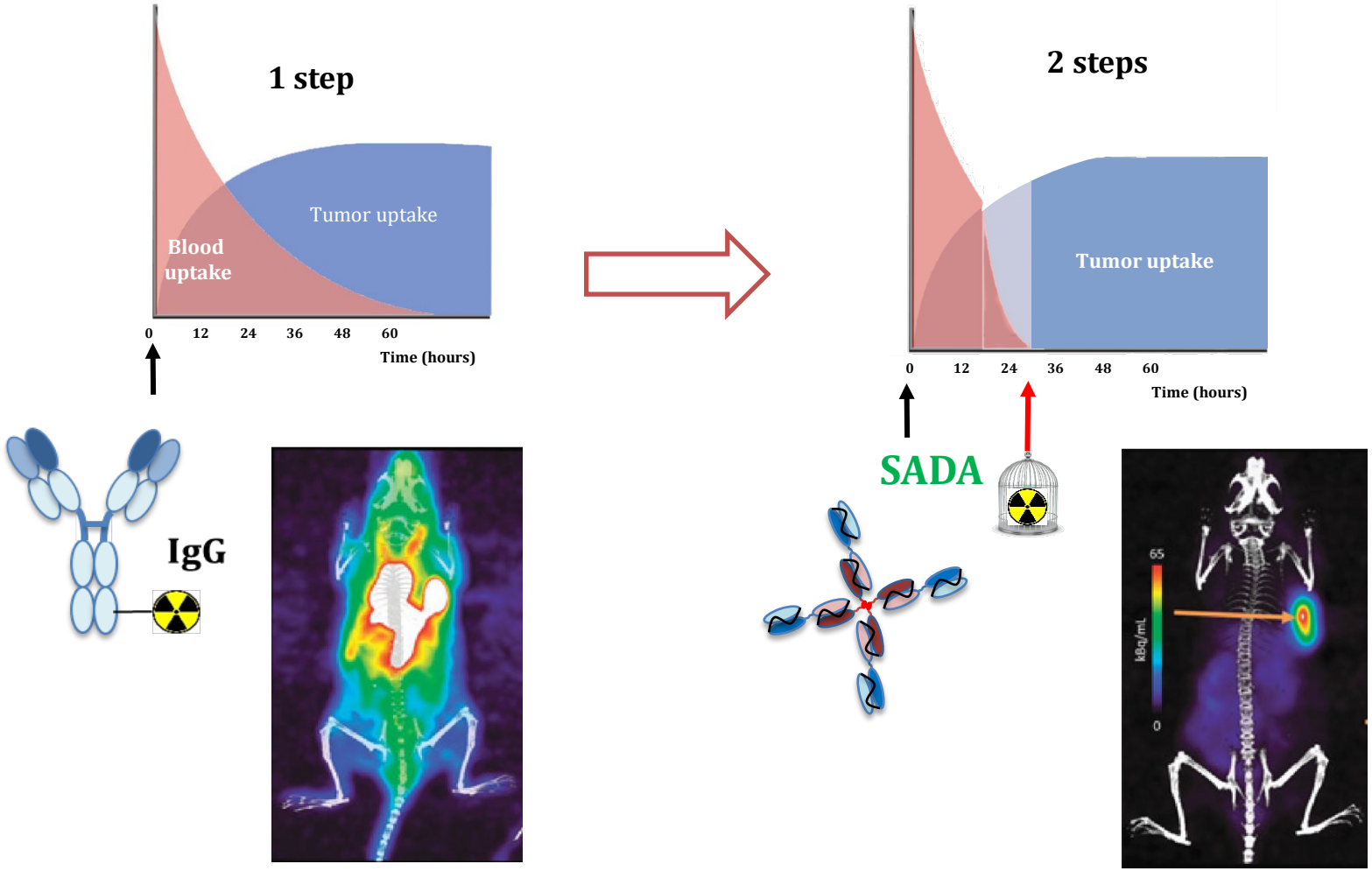


Ferreira et al, PMID: 40475779

SADA

SADA Pretargeted Radioimmunotherapy (SADA-PRIT)

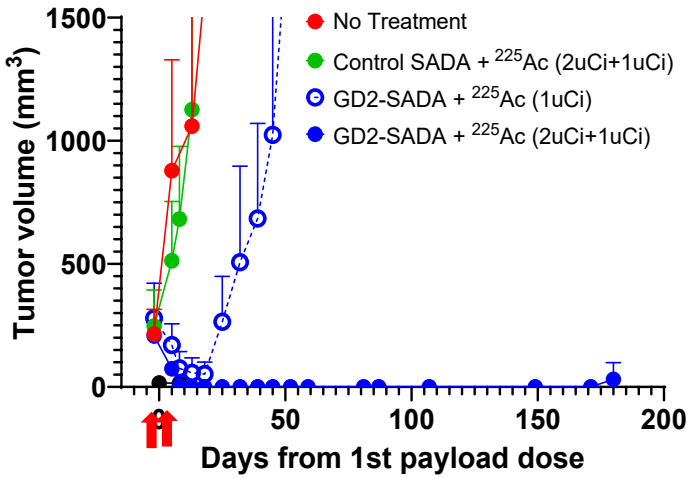
2 steps instead of 1 step

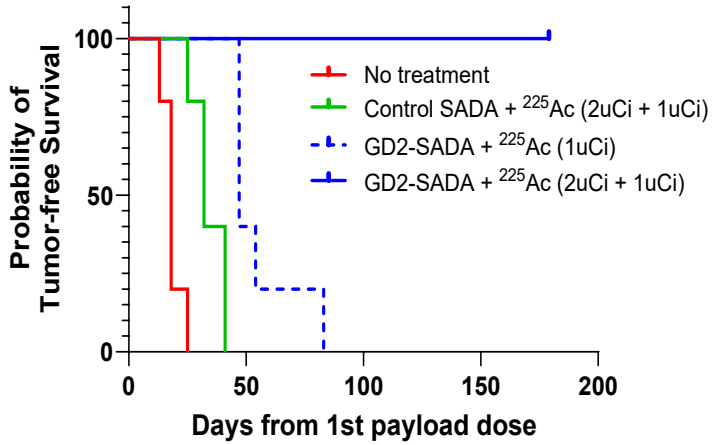


Complete Response and Durable Remission after one cycle of therapy

Neuroblastoma Xenograft

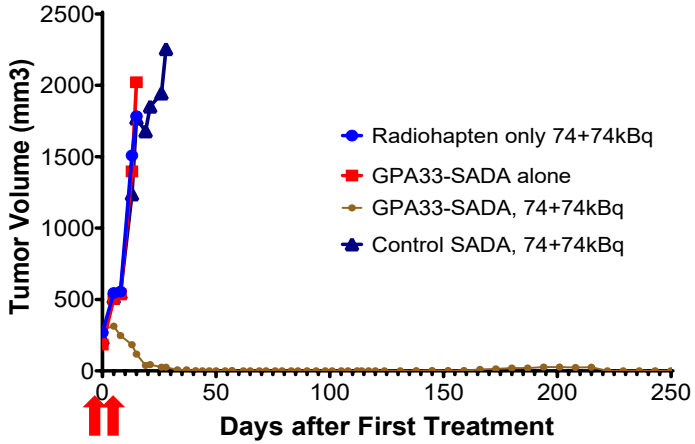
74+37 kBq = 5.1 MBq/kg

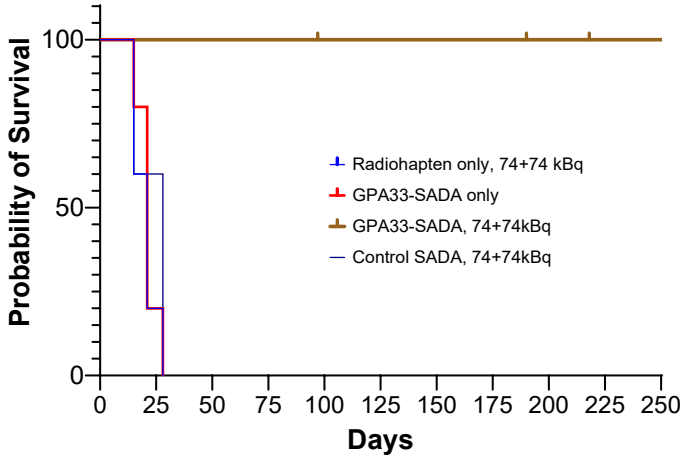




Colon Cancer Xenograft

74+74 kBq = 6.8 MBq/kg





Sparing Innocent Bystanders

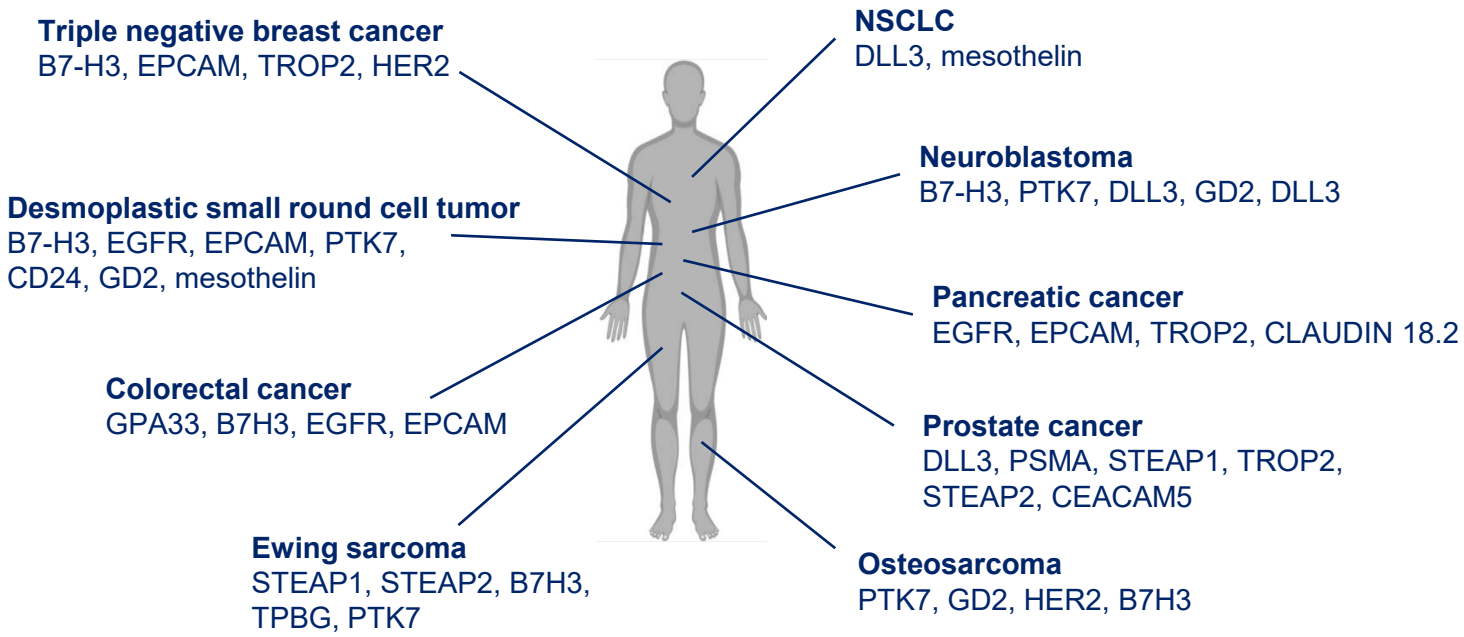
Summary of Mouse Histology	180 mCi/kg, BRG, Male Day120 - ^{177}Lu	40 uCi/kg, BRG, Male Day 120 - ^{225}Ac
Alimentary System - Stomach, Duodenum, jejunum, ileum, Cecum, Colon, Salivary Glands, Esophagus, Teeth, Oral Cavity,	*NS	*NS
Cardiovascular System - Heart	Normal	Normal
Endocrine System - Adrenals*	Normal	Normal
Endocrine System - Pancreas, Thyroid, Parathyroid, Pituitary Gland	Normal	Normal
Hepatobiliar System - Liver, gallbladder	Normal	Normal
Immune System - Spleen, Mesenteric LN, Submandibular LN, Thymus, Bone marrow,	*NS	*NS
Nervous System - Brain, Spinal cord, hind limb nerve, spine	Normal	Normal
Other - Skin (trunk), Ears	*NS	*NS
Reproductive System - Ovaries*	NA	NA
Reproductive System - Uterus, Cervix, Perigenital skin, Vagina, Oviducts, Mammary glands,	Normal	Normal
Respiratory System - Lungs, nasal cavity, trachea	*NS	*NS
Skeletal System - Skull, Femur, Tibia, Sternum, Vertebrae, Stifle joint	Normal	Normal
Skeletral muscles (hind limb, spine)	Normal	Normal
Urinary System - Bladder*	Urothelial degeneration, necrosis, hyperplasia, ulceration, and fibrosis	Normal
Urinary System - Kidneys	*NS	*NS
Visual System - Eyes, harderian gland, lacrimal gland	Normal	Normal

***NS = nonspecific changes observed also in untreated littermates**

Technology Evolution
PRIT Step #1

Targeted Payload Engager Platform for other targets and tumors

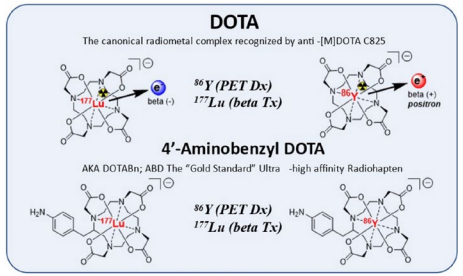
- **Purpose:** To Widen the Therapeutic Window
- **Metrics:**
  - Curative after 1-2 cycles
  - Durable remission >= 6 months in CDX and PDX models
  - No Dose Limiting Toxicities
- **Tools:**
  - Multispecific antibodies
  - 2-step Pretargeting
  - Radioisotopes (α,β,e+)



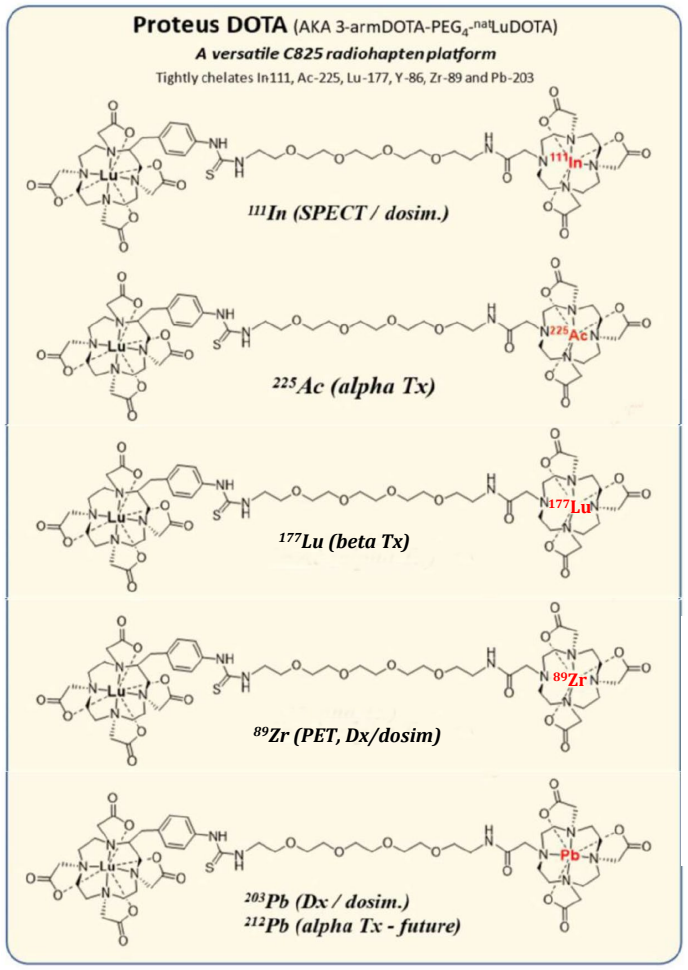
Technology Evolution
PRIT Step #2

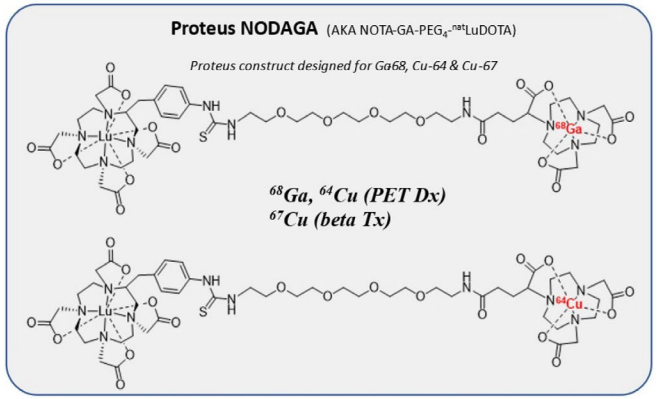
Innovations for STEP #2

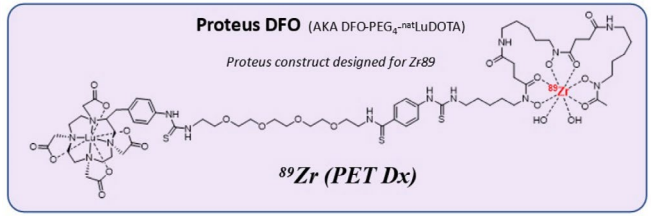
1st Generation
(One DOTA - univalent)

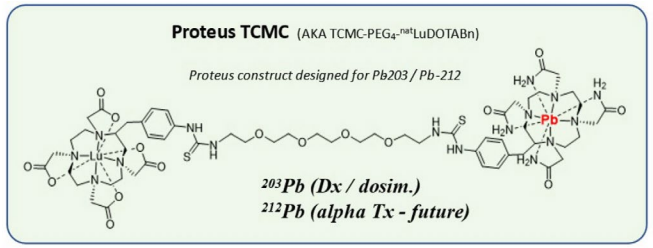


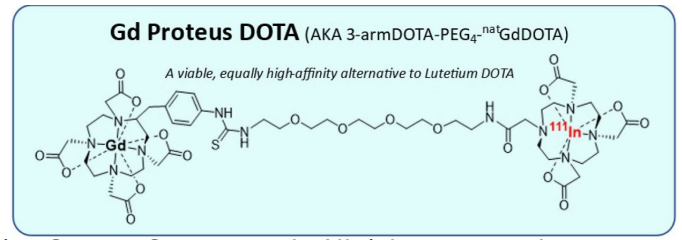
2nd Generation
(One BnDOTA - univalent)



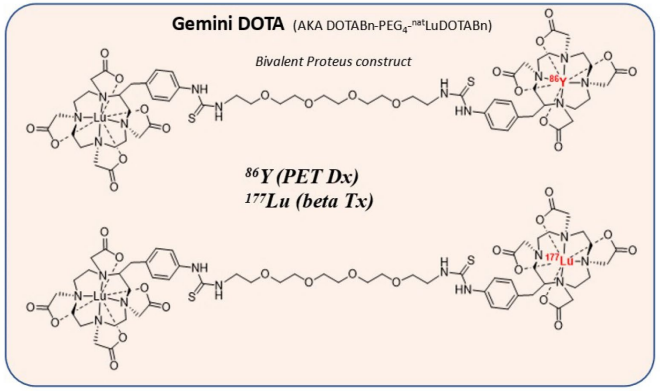


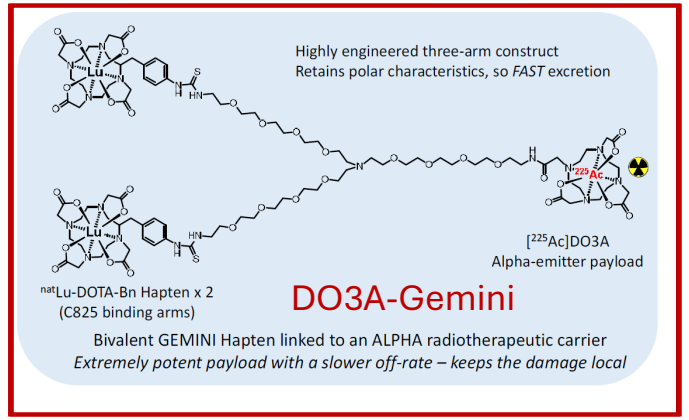






3rd Generation
(Two BnDOTAs - Bivalent)





Three generations of DOTA payloads validated for TPE with body clearance (mice and primates) similar to 1st generation DOTA, avoiding trapping in blood, kidney, liver or the reticuloendothelial system (RES), except Proteus DFO, the only ligand with renal trapping.