“Affinity cocktails” of alpha-particle radionuclide antibody-conjugates for solid tumors

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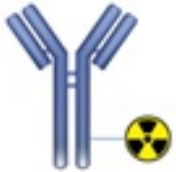
CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025

NEXT-GENERATION DELIVERY INNOVATIONS

Rationale

Goal: Optimize targeted alpha-particle therapeutics (TAT) by enabling their deep penetration in solid tumors



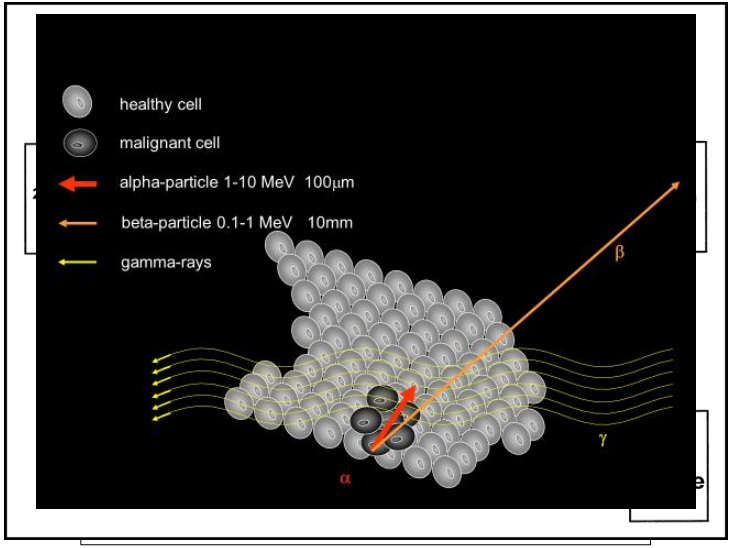
TAT are currently experiencing a renaissance

before 2016: 1 clinical trial

2024: 20 active clinical trials - 70% involving antibody-radioconjugates

α-particle RadioPharmaceutical Therapy

- Alpha-particles are high-energy, short-range particles that travel in tissue up to 40-80 μm, emitted from radionuclides, that physically impair DNA as they traverse the cell nucleus.
- The pattern of tumor irradiation matters: cells not being hit by α-particles will most likely not be killed and can lead to recurrence.
- **The α-particle emitter ^{225}Ac (Actinium-225) decays to ^{209}Bi (Bismuth 209) emitting 4 α-particles.**
- They transverse tissue, produce complex double strand breaks in DNA that overwhelm cellular repair in the diseased tissue.
- Partial tumor irradiation is the root cause of treatment failure with α-particle therapy.
- Effectiveness is largely independent of cell cycle and oxygen concentration.
- Alpha-particles have limited penetration in tissue sparing adjacent healthy tissues.



McDevitt et al. 2018 *Annual Review of Biomedical Engineering*
Kassis and Adelstein et al. 2005 *Journal of Nuclear Medicine*
Sofou et al. 2004 *Journal of Nuclear Medicine*

Rationale Description

Why TAT works?

The enthusiasm for TAT is due to the unparalleled **killing efficacy** of, and **irradiation precision** by, alpha-particles, **AND** the **selectivity in tumor targeting** by antibody technologies.

Problem to solve

Treated patients ultimately relapse.

Targeting (“high-affinity”) antibodies do not penetrate solid tumors.
Cells not being hit by short-range TAT will not be killed.

Our goal: improve TAT penetration using cocktails of antibodies of variable affinities.

Our Approach

Antibody “affinity cocktails”

uniformly distribute α-particles within tumors by **simultaneously delivering the same α-particle emitter by antibodies of different affinity, each killing a different region of the tumor**:

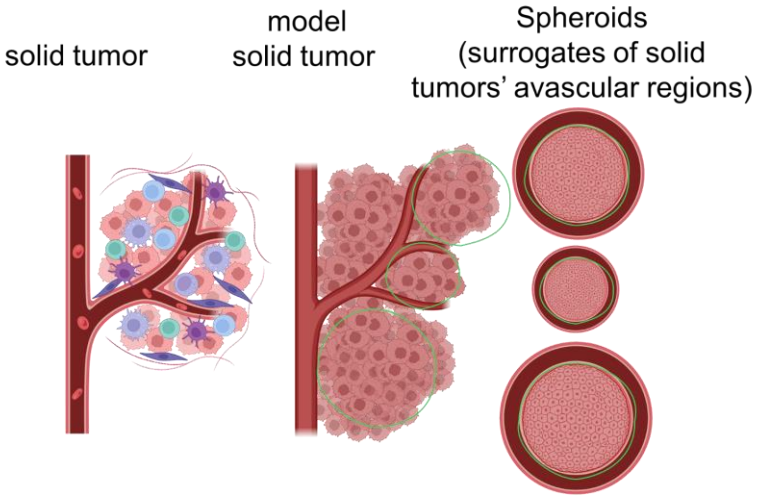
(1) a **“high-affinity” radiolabeled-antibody** (this will soon become the **“new standard of care”**) irradiating the **tumor perivascular regions** and

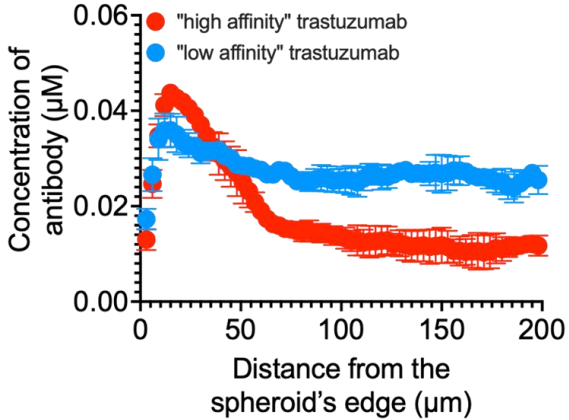
(2) a separately administered **“low(er)-affinity”(form of the same) radiolabeled-antibody** that upon tumor uptake penetrates the **deeper parts of tumors** where “high-affinity” antibodies do not reach, **but clears too fast from the tumor perivascular regions**

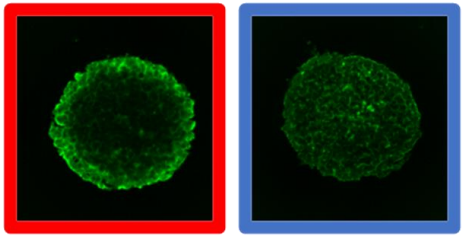
Our Approach

3D multicellular spheroids of cancer cells

Established Model: to characterize the extend of penetration of radioconjugates





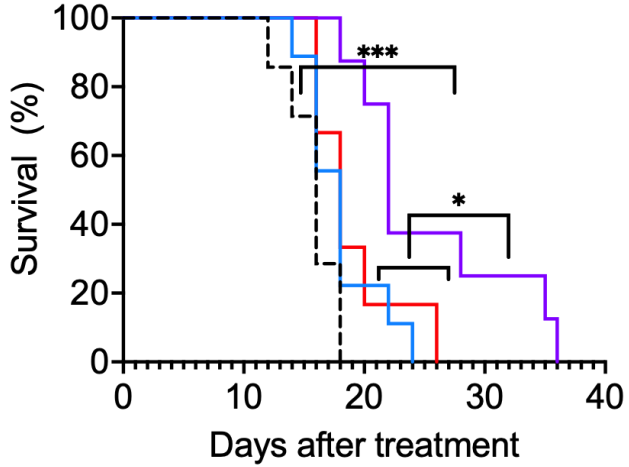


"high affinity" trastuzumab

"low affinity" trastuzumab

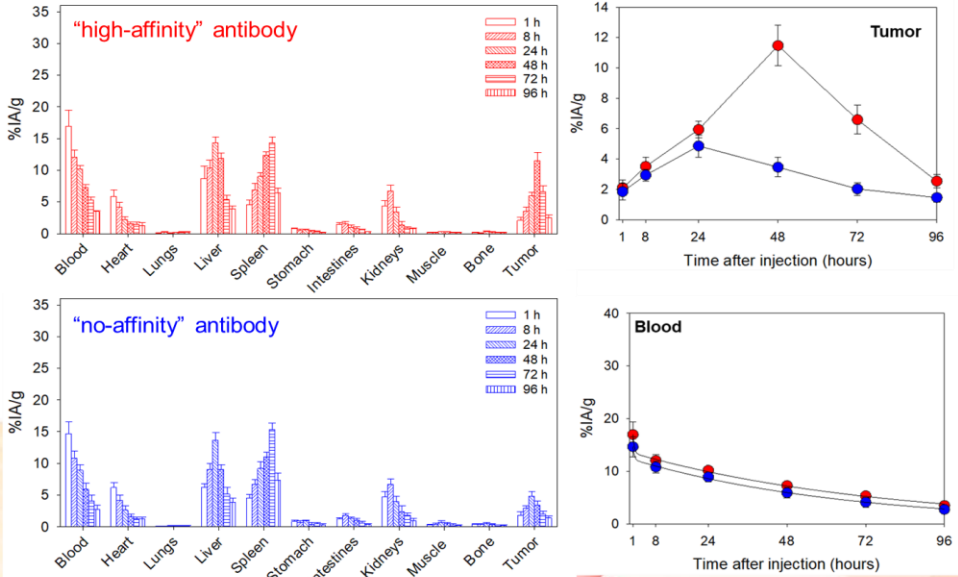
Proof-of-concept: moderately-expressing HER2 subcutaneous tumors

EFFICACY: Longer Survival with “affinity cocktails” of antibody-radioconjugates compared to “high-affinity” antibody-radioconjugates at **same total injected (radio)activity**



- no Treatment (n = 7)
- 100% “high - affinity" trastuzumab (n = 6)
- 100% "low - affinity" trastuzumab (n = 9)
- 50% : 50% "high - affinity" : "low - affinity" trastuzumab (n = 9)

TOXICITY: Off-target uptake/dosimetry: are identical for the high-affinity antibody and low-affinity/“no-affinity” antibody



General applicability of our technology

Antibody “affinity cocktails” are a general approach for Targeted Alpha-particle radionuclide Therapeutics

independent of :

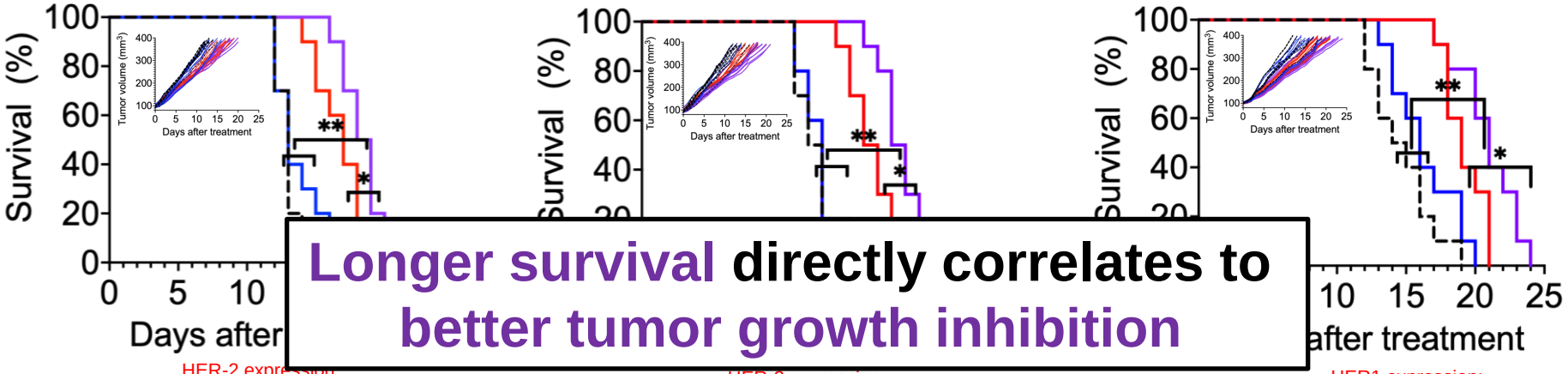
- tumor origin, and/or
- expression levels of targeted markers

General applicability of our technology: tumor origin and marker expression

BT474 **HER2+ breast** cancer

HEPG-2 moderately **HER2** expressing **hepatic** cancer

BxPC-3 low **HER1** expressing **pancreatic** cancer



Longer survival directly correlates to better tumor growth inhibition

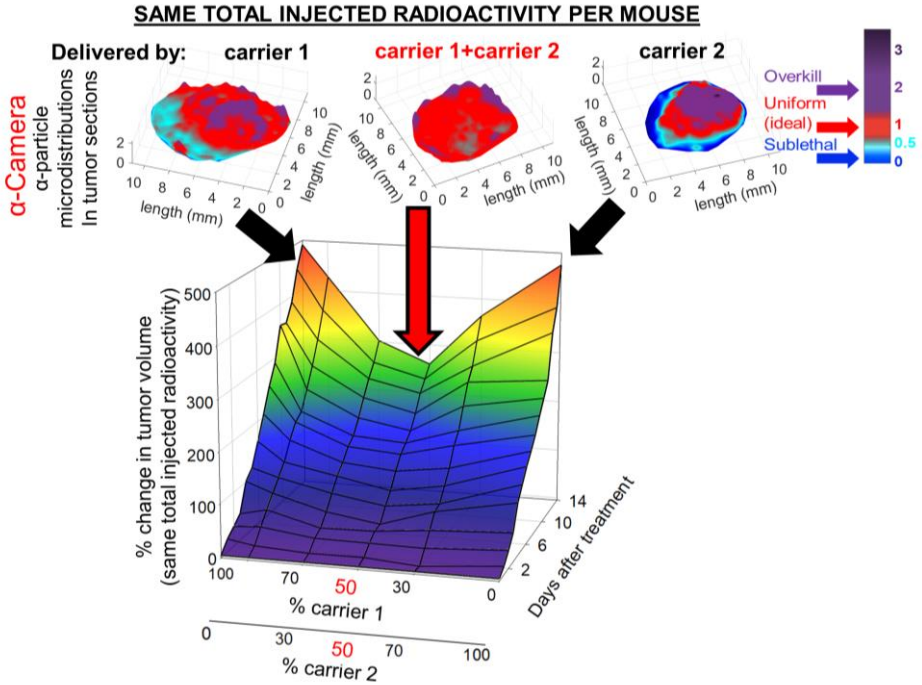
** - p < 0.05*
*** - p <0.01*

Decreasing expression levels of targeted markers

“patterning matters”:

more uniform microdistributions of α-particles in tumors

enable better inhibition of tumor growth **even at lower tumor delivered doses**



Journal of Nuclear Medicine 63 (8), 2022,1223-1230
Featured basic science paper

Bioengineering & Translational Medicine 7 (2), 2022, e10266

Key findings and conclusions

- spatiotemporal control of drug deposition in solid tumors guides treatment efficacy

- can be achieved by combinations of diverse, separate delivery carriers, chosen to kill complementary regions of the same tumor
  (it's the carrier "properties" that matter not the "chemistry")

Acknowledgements

Sofou Lab Members

Dr. Rajiv Ranjit Nair
Pooja Hariharan
Rohit Chaudhari

Collaborators

Mihalis Kavousanakis, NTUA
Yannis Kevrekidis, JHU
Remco Bastiannet, WUSTL
Roger Howell, Rutgers University
George Sgouros, JHMI
Zaver Bhujwalla, JHMI
Anders Josefsson, JHMI
Kathy Gabrielson, JHMI

Funding Sources

CDMRP; Hartwell Foundation; TEDCO MII; AHN-Cancer Research Fund; WW Smith Charitable Trust; NSF; Elsa Pardee Foundation; Walsh Research Award; DoE Isotope Program/ ORNL

*The actinium-225 used in this research was supplied by the U.S. Department of Energy Isotope Program managed by the Office of Isotope R&D and Production


QUESTIONS
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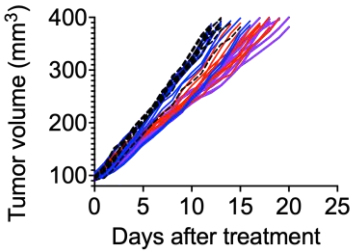
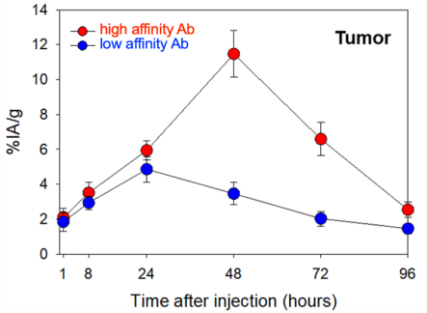
Appendix

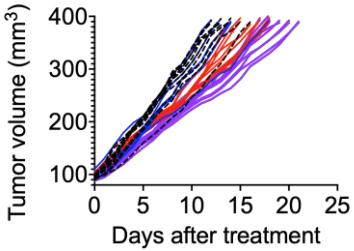
General applicability of our technology

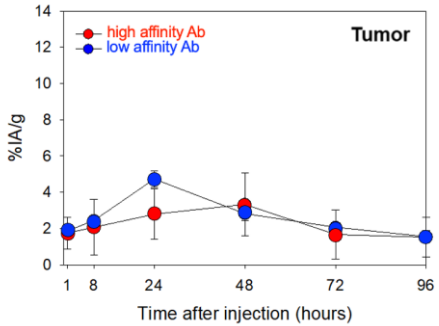
BT474 **HER2+ breast** cancer



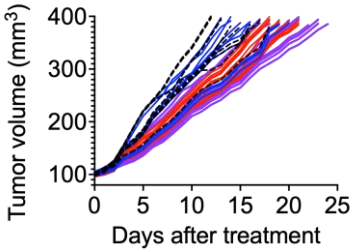


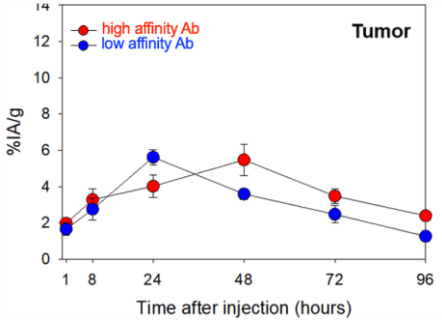
HEPG-2 moderately **HER2** expressing **hepatic** cancer





BxPC-3 low **HER1** expressing **pancreatic** cancer





- No Treatment (n = 10)
- 100% high affinity antibody radioconjugate (n = 10)
- 100% low affinity antibody radioconjugate (n = 10)
- 50%:50% high affinity: low affinity antibody radioconjugate (n = 10)

General applicability of our technology

Organ	Absorbed Dose (Gy)*	
	Delivered by "high-affinity" antibody	Delivered by "no-affinity" antibody
Heart	0.6 ± 0.3	0.5 ± 0.1
Lungs	0.0 ± 0.0	0.0 ± 0.0
Liver	0.3 ± 0.0	0.4 ± 0.0
Spleen	5.0 ± 0.3	5.1 ± 0.3
Kidneys	0.2 ± 0.0	0.3 ± 0.0
Intestine	0.0 ± 0.0	0.0 ± 0.0
Stomach	0.0 ± 0.0	0.0 ± 0.0
Bone	0.0 ± 0.0	0.0 ± 0.0
Muscle	0.0 ± 0.0	0.0 ± 0.0
*Calculated for 2.96 kBq injected activity of actinium-225		