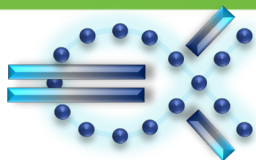


Actinium-225 & Bismuth-213: Two Important Alpha Emitters for the Future of Therapeutics

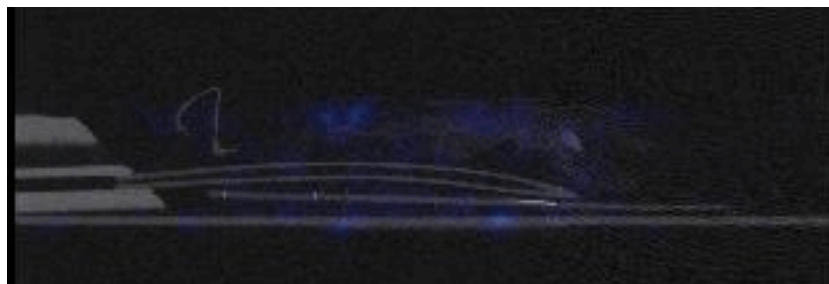
radimmune
Therapeutics



Actinium
Pharmaceuticals, Inc.



This research is supported by the U.S. Department of Energy Isotope Program,
managed by the Office of Science.



Kevin Allen, PhD

July 28th, 2020

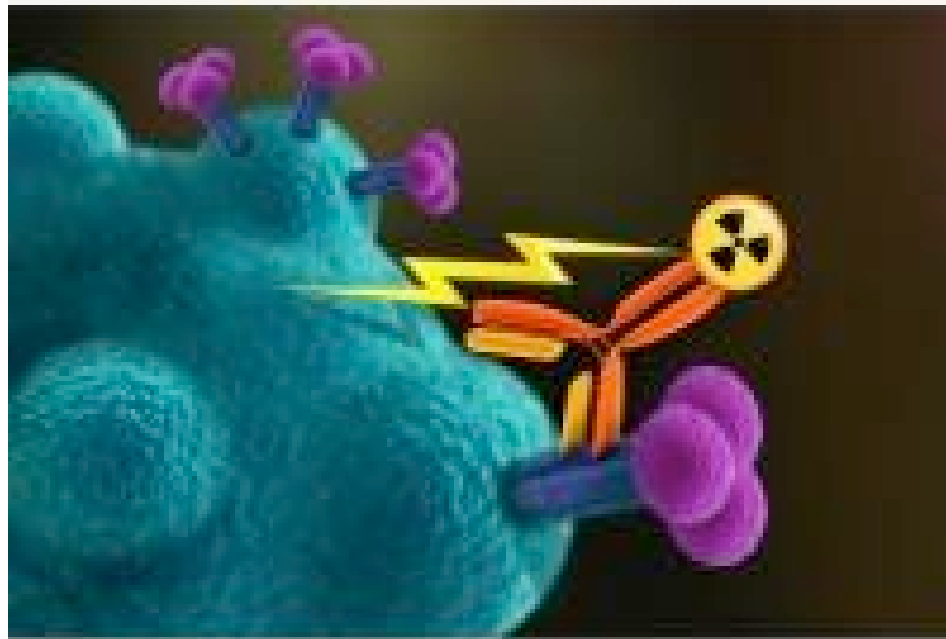
Actinium-225 DOE Users Meeting

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Radioimmunotherapy (RIT)

Tumor specific antibodies direct radionuclides to cancer cells

RIT limits the dose to normal tissues

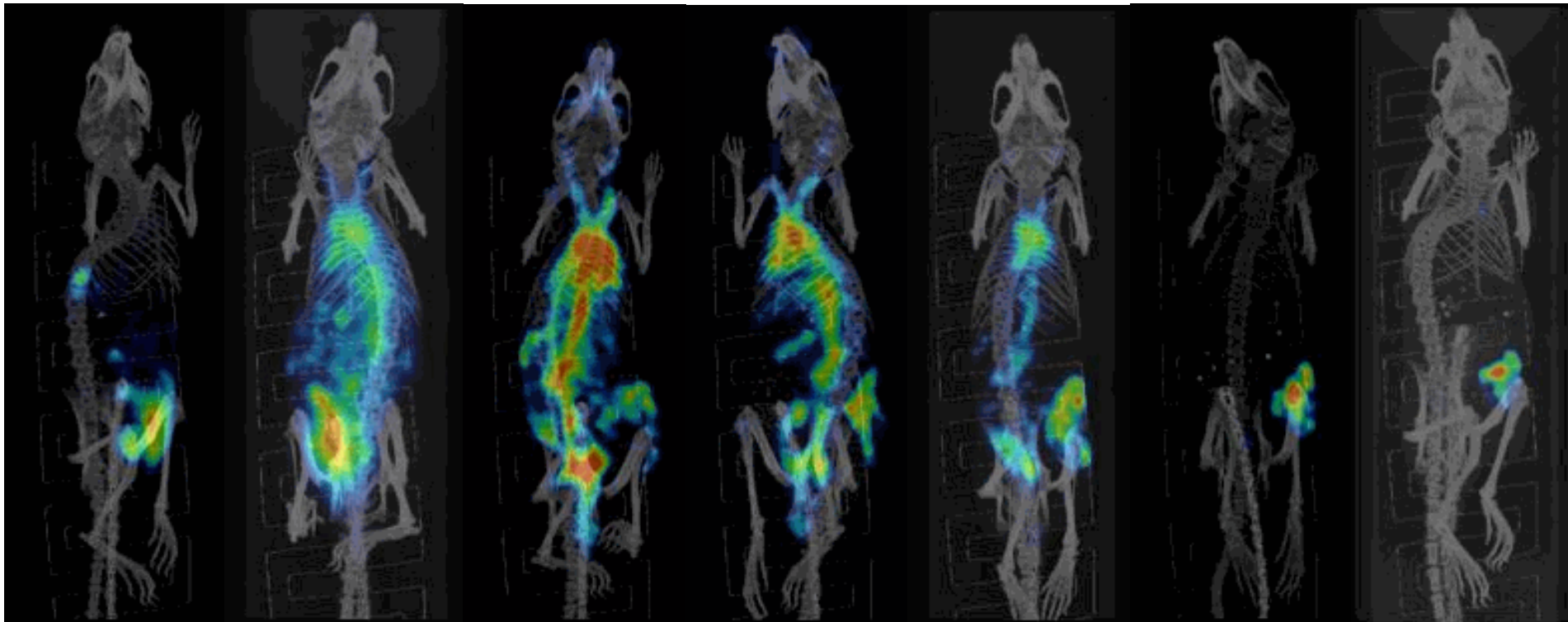


Daratumumab

- Anti-CD38 monoclonal antibody approved for treatment of multiple myeloma
- CD38-therapeutic antibodies rely on classical on Fc-dependent mechanisms – antibody dependent cellular toxicity, antibody dependent cellular phagocytosis, and compliment dependent cytotoxicity
- Not all patients respond to treatment...can it be improved with radioactivity?

Imaging of Daudi Tumor Bearing Mouse with ^{111}In Labeled Daratumumab

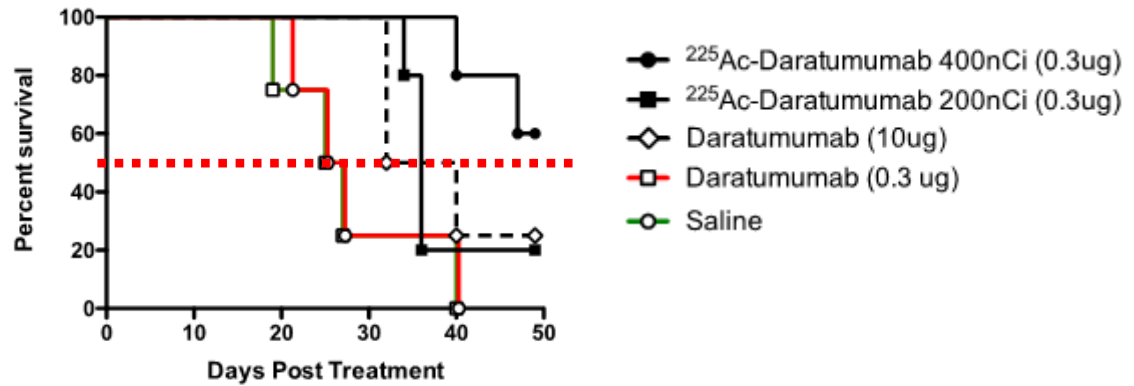
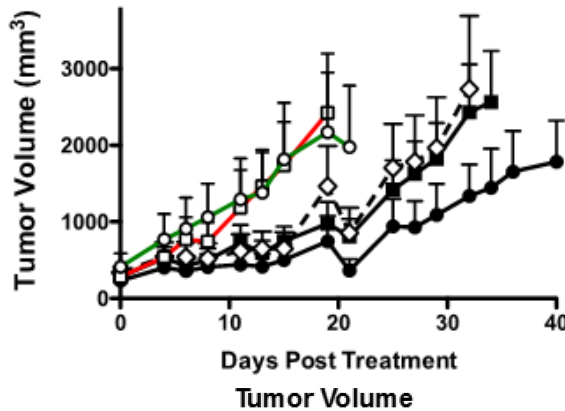
1h 4h 24h 48h 72h 168h 240h



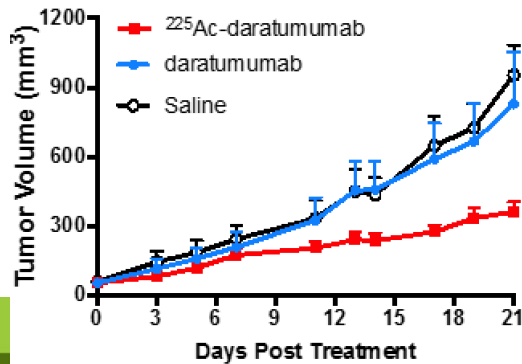
^{225}Ac Labeled Daratumumab

Targeting is effective, but will it translate into an increase in efficacy?

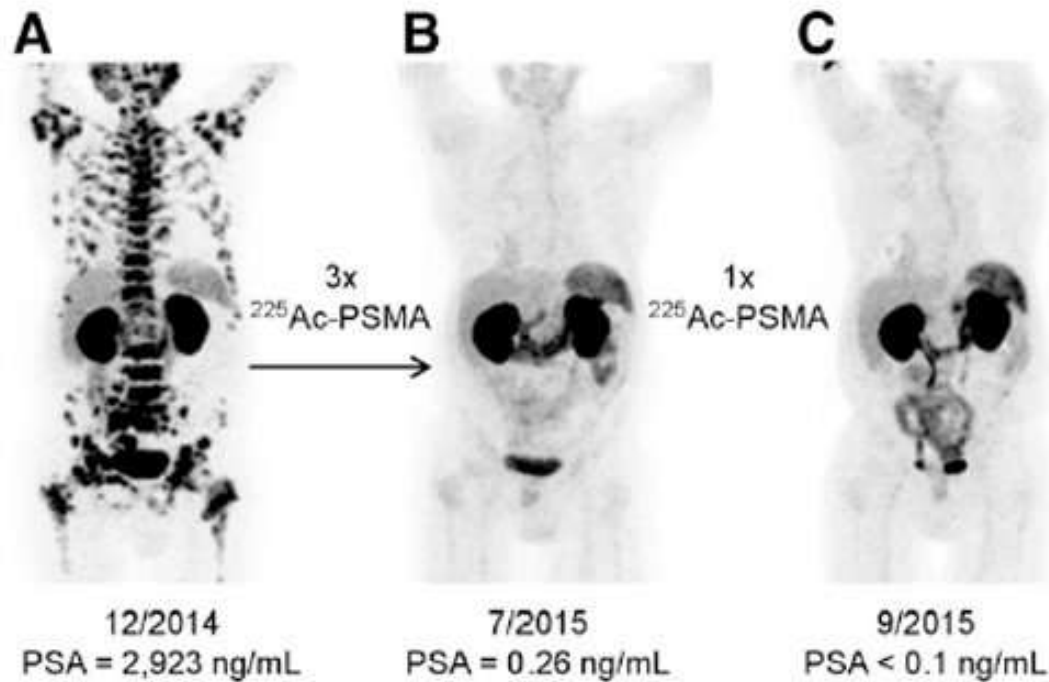
Daudi



KMS-28-BM

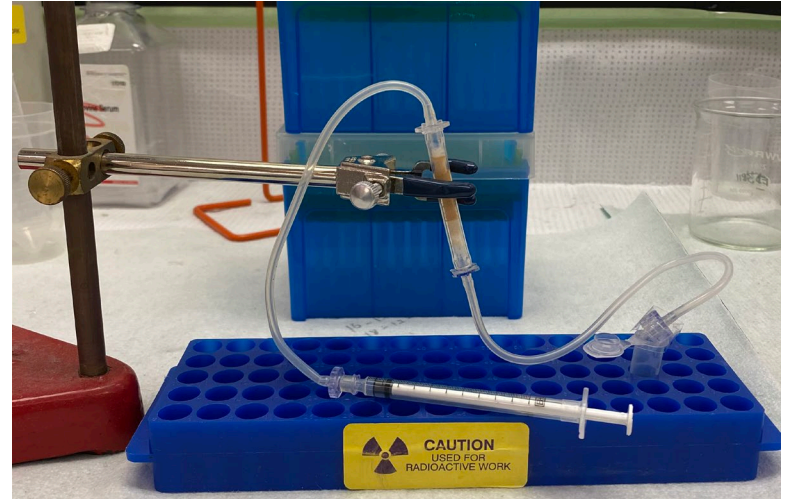


Is Actinium Always the Answer?



Bismuth-213

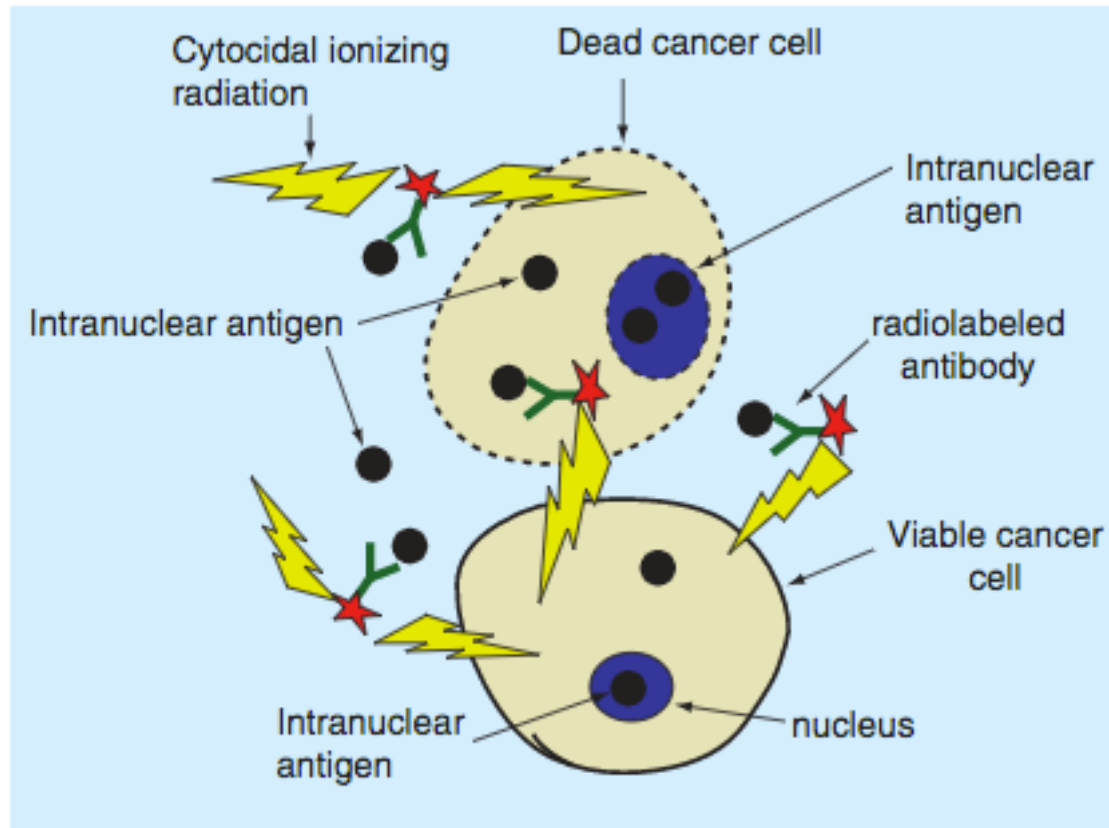
- Short physical half-life (~46 minutes)
 - Advantage or Disadvantage?
- Eluted from $^{213}\text{Bi}/^{225}\text{Ac}$ generator
 - Elution time
 - Reaction time
 - Purification time
- Troubleshooting
 - Occasionally decreased labeling % over time



Melanoma

- Approximately 100,350 new cases in 2020 (60,190 male, 40,160 female) with 6,850 deaths (4,610 male, 2,240 female) in the United States
- Good prognosis with early detection (>90%)
- Late stage metastatic melanoma has very poor survival rate (10-15%)

Melanoma Targeting Strategy



Imaging of B16F10 Melanoma Tumor Bearing Mouse with ^{111}In Labeled h8C3 Antibody to Melanin

1h

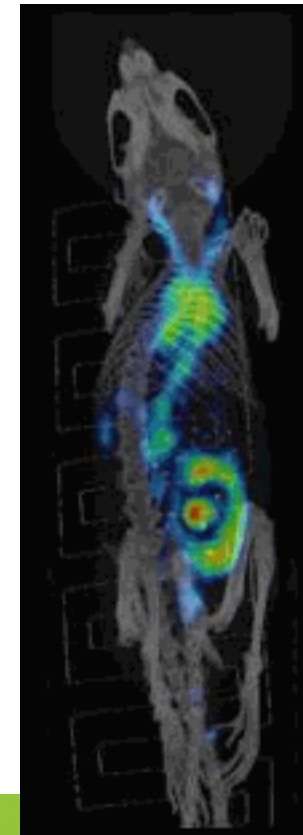
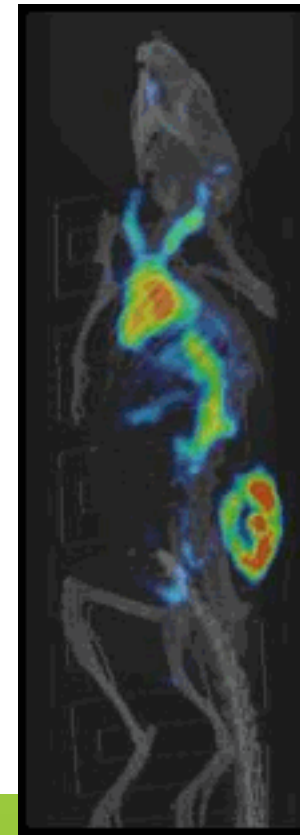
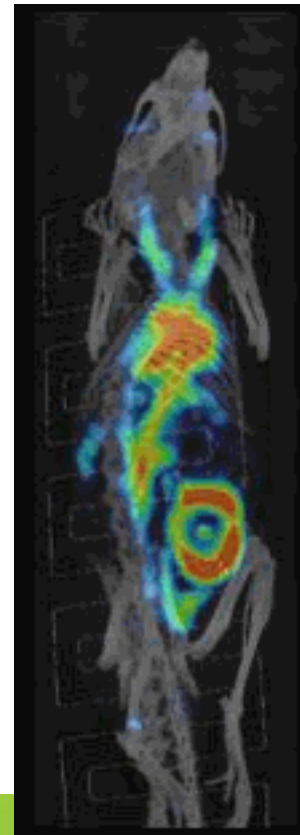
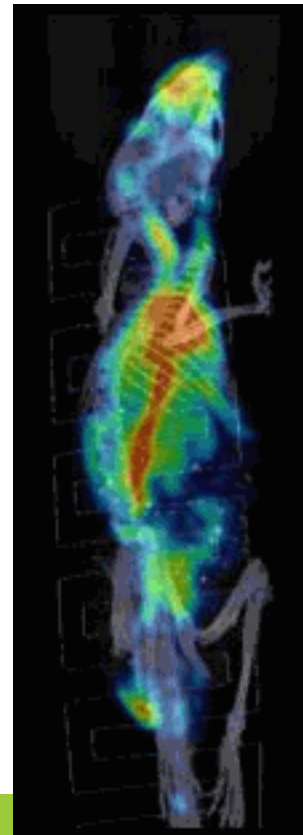
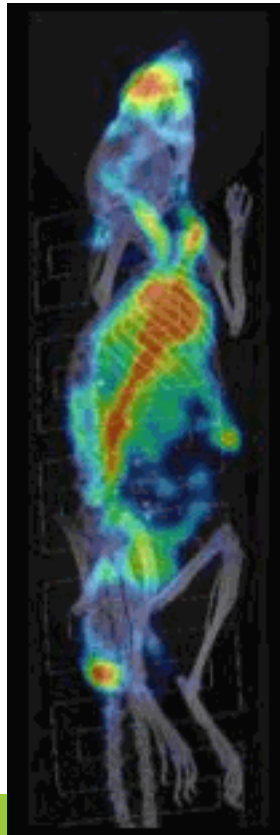
2h

4h

24h

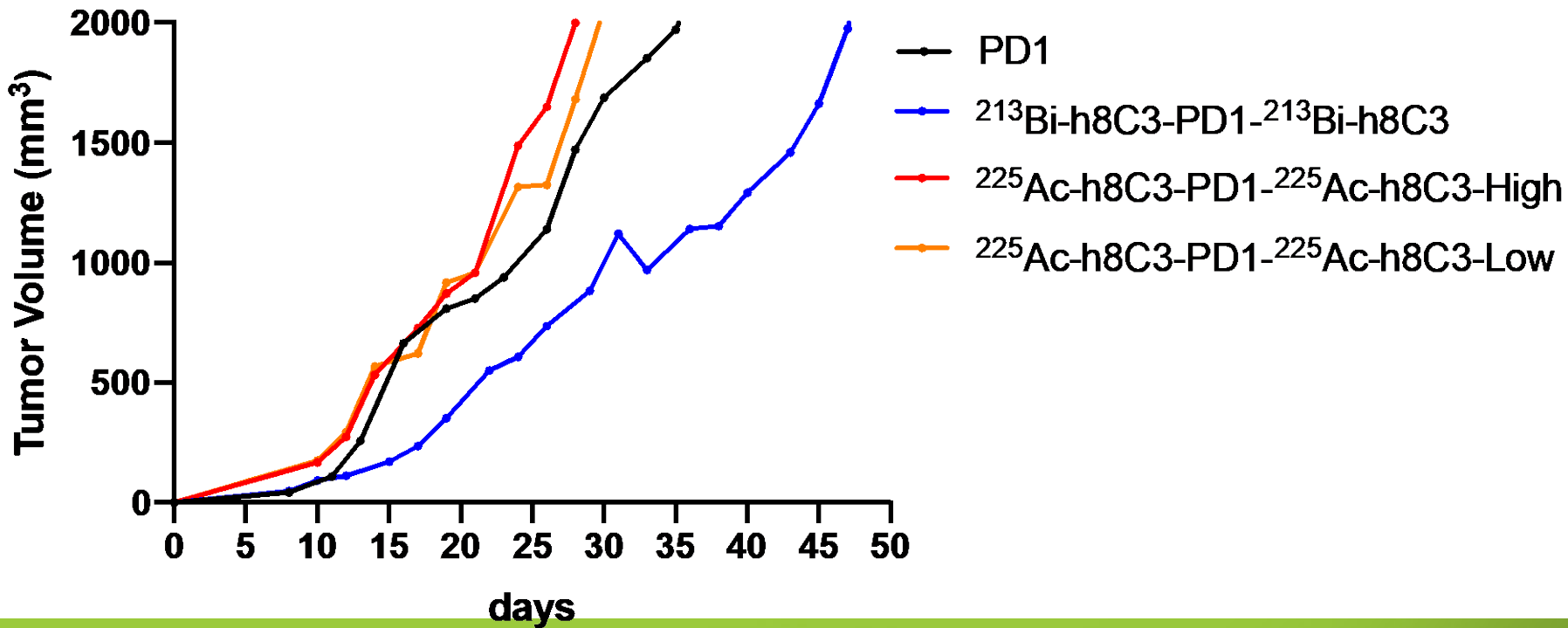
48h

72h

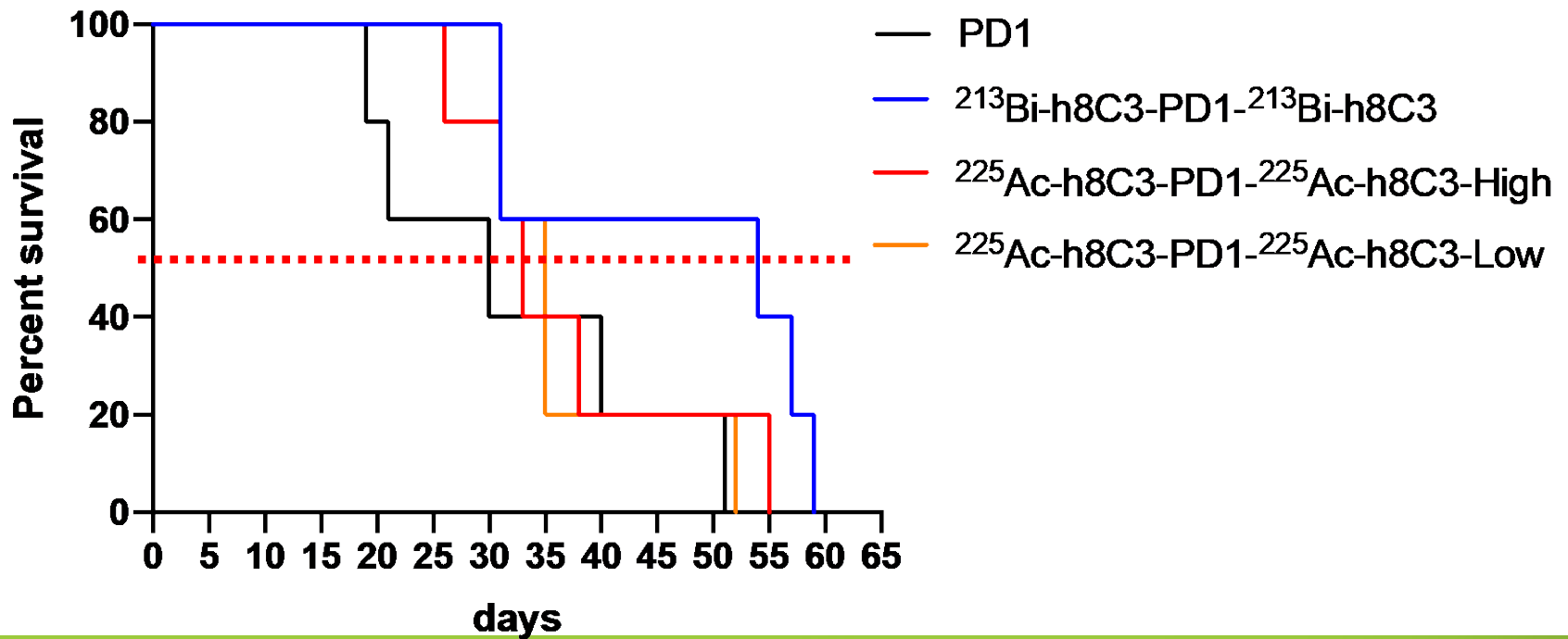


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Comparison of ^{213}Bi -h8C3 & ^{225}Ac -h8C3 Antibodies to Melanin in Combination with Immunotherapy in Cloudman S91 Melanoma Tumor Bearing Mice



Kaplan-Meier Survival Graph for Comparison between ^{213}Bi -h8C3 & ^{225}Ac -h8C3 Antibodies to Melanin in Combination with Immunotherapy in Cloudman S91 Tumor Bearing Mice

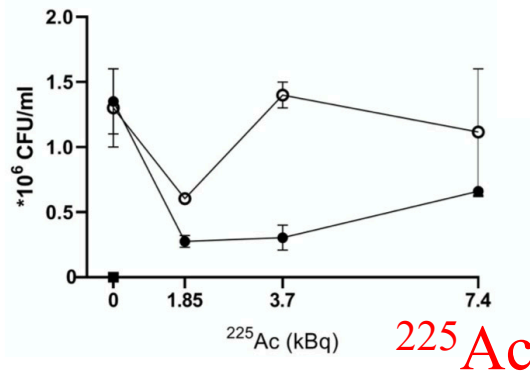


RIT for Treatment of Infected Prosthetic Joints

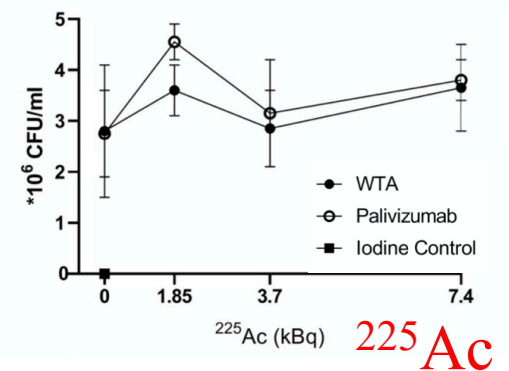
4497 antibody targets wall teichoic acids (WTAs) that are present both in bacteria and biofilms of methicillin-resistant *staphylococcus aureus* (MRSA)

Labeling 4497 with ^{225}Ac , and ^{213}Bi shows the different properties of each radioisotope showing that only ^{213}Bi is effective at eliminating both active MRSA bacteria and the difficult to treat biofilms film composed of dormant bacteria.

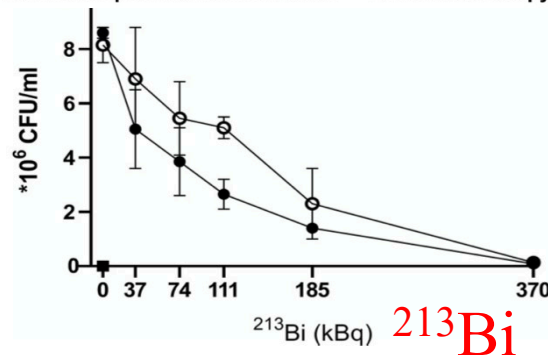
Survival of planktonic MRSA after ^{225}Ac -immunotherapy



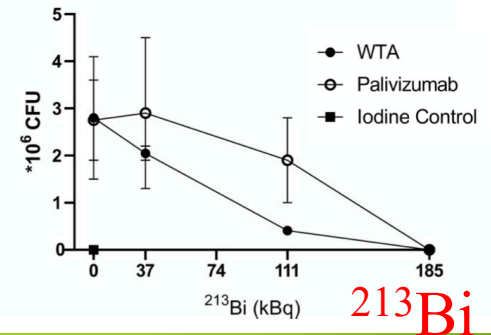
Survival of MRSA biofilm after ^{225}Ac -immunotherapy



Survival of planktonic MRSA after ^{213}Bi -immunotherapy



Survival of MRSA biofilm after ^{213}Bi -immunotherapy



Summary

- ^{225}Ac is extremely potent radionuclide which can greatly enhance the therapeutic potential of small molecules and biologics alike
- In some cases, such as very aggressive cancers or fast proliferating infections, ^{225}Ac low decay rate which is due to its long physical half-life becomes a disadvantage. In such cases its daughter ^{213}Bi seems to be a more effective alternative
- Large quantities of ^{225}Ac are needed for the advancement of radiotherapeutics

Acknowledgements:

Group members

Mackenzie Malo
Rubin Jiao
Wojciech Dawicki
Bruce Van Dijk
Ravendra Garg
Connor Frank
Jaline Broqueza
Muath Hilal

Supervisor

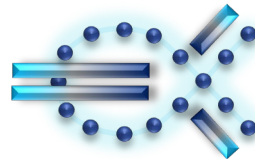
Dr. Kate Dadachova



National Institutes
of Health
SBIR/STTR



This research is supported by the U.S. Department of Energy Isotope Program, managed by the Office of Science.



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