Boston Children's Hospital

A Possible Theranostic Approach to Treating Metastatic Neuroblastoma

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USDOE August 2021

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Disclosures

Clarity Pharmaceuticals

(Research Funding)

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Neuroblastoma

- The second most common solid malignancy in children
- Small number of patients
  - 650 to 700 new cases/y in the US*
- Average age at first presentation – 19 months
- Frequently diagnosed at later stages (stage 3-4)
- Early treatments are effective, but patients frequently (>75%) relapse with widespread metastatic disease
- Survival rate of patients with relapsed disease is extremely low
- Can we improve their prognosis?

*http://www.cncfhope.org/CNCF_FAQs

Neuroblastoma: Possible Targets

SSTR2

- Present on up to 90% of NB tumors
- Octreotide derivative
- High binding affinity
- Peptide
- ^{68}Ga-DOTATATE (NETSPOT) approved for imaging adult somatostatin-receptor positive neuroendocrine tumors
  - Not extensively evaluated in neuroblastoma
- ^{177}Lu-DOTATATE(Lutathera) approved for treating adult somatostatin-receptor positive neuroendocrine tumors
  - Not extensively evaluated in neuroblastoma

SSTR2 Receptor

Why look beyond ^{68}Ga-DOTATATE (NETSPOT) and ^{177}Lu-DOTATATE (Lutathera)?

^{68}Ga-DOTATATE

- High cost of the ^{68}Ge/^{68}Ga generator
- Availability of the ^{68}Ge/^{68}Ga generator
- Low resolution of ^{68}Ga images
- Short half-life of ^{68}Ga limits the ability to do dosimetry calculations

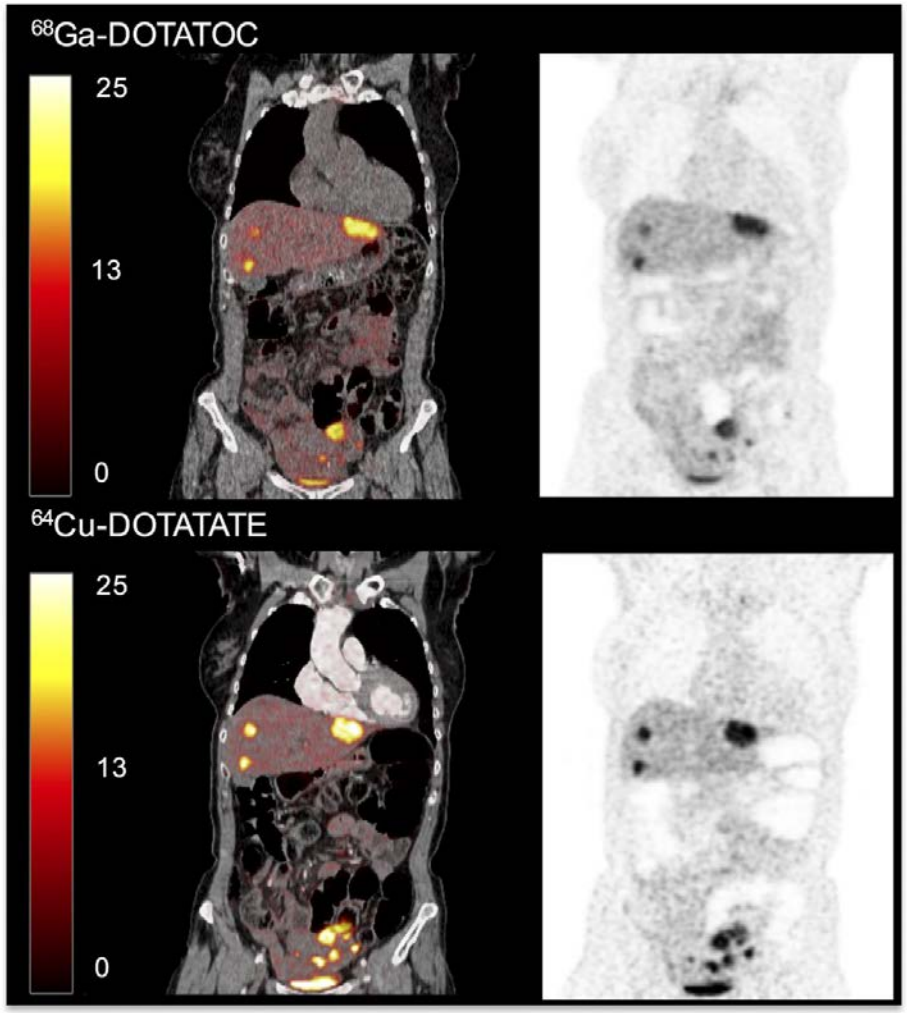
^{177}Lu-DOTATATE

- Not a matched pair with ^{68}Ga-DOTATATE

^{64}Cu-DOTATATE vs. ^{68}Ga-DOTATOC

PET/CT (left) and PET (right) scans of patient with intestinal NET and multiple metastases.

More lesions are seen in intestinal region with ^{64}Cu-DOTATATE than with ^{68}Ga-DOTATOC.



Johnbeck, et al. *J Nucl Med* 2017;**58**:451-457

Imaging: ^{68}Ga versus ^{64}Cu

^{68}Ga

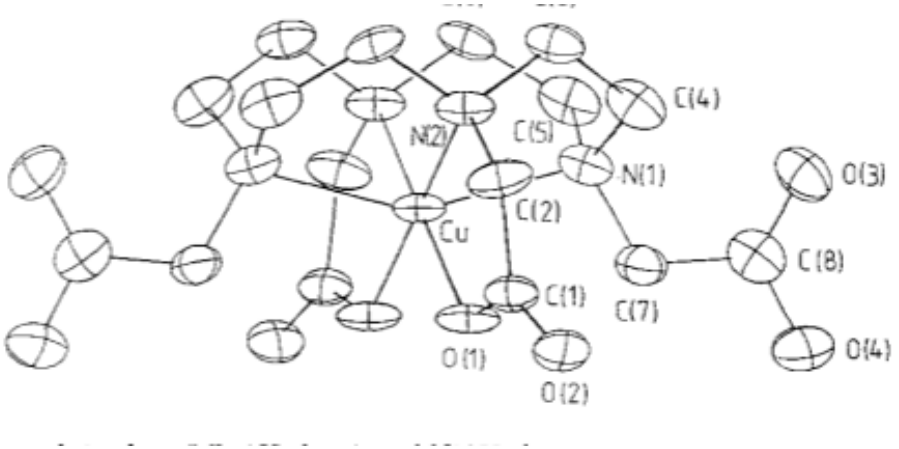
- $T_{1/2}$ = 68 min
- β^+ Yield: 88.9%
- β^+_{mean} = 836 keV
- Positron range: 4 mm
- Production – ^{68}Ge/^{68}Ga generator, cyclotron
- Shippable? No

^{64}Cu

- $T_{1/2}$ = 12.7 h
- β^+ Yield: 17.6%
- β^+_{mean} = 278 keV
- Positron range: 1 mm
- Production – cyclotron
- Shippable? Yes
- Very labile

"Better" Chelator for Copper

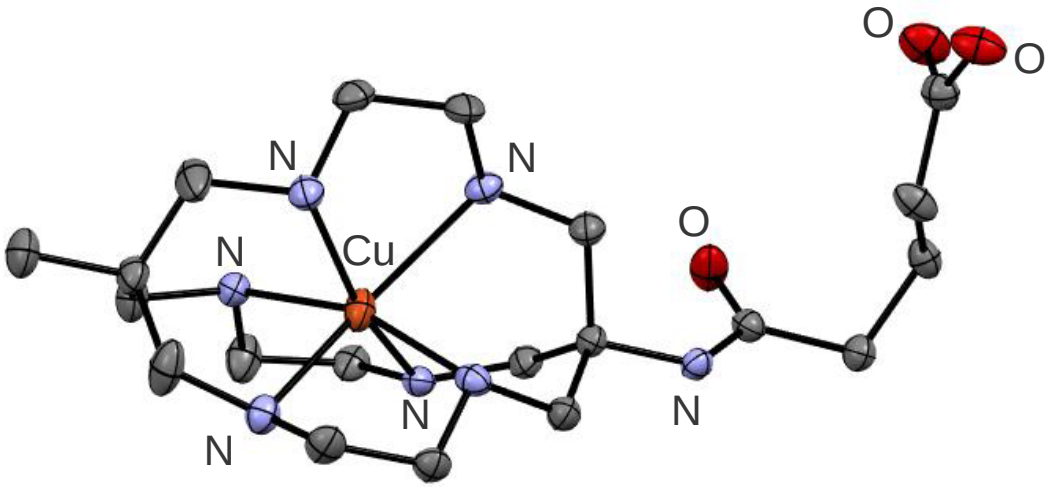
Cu-DOTA



A.Riesen, et al. *Helv Chim Acta* **69**, 2067 (1986)

- Cu doesn't fit within the core
- *pba* tail for binding to proteins
- Easy to make $^{64/67}$Cu complex
  - (acetate buffer, RT)
- Cu(II) lost from complex *in vivo*

Cu-MeCOSar



Donnelly *et al.*, *Dalton Trans.,* **2014,** 43, 1386

- Derivative of diamsar
- -COOH tail for binding to proteins
- Easy to make $^{64/67}$Cu complex
  - (acetate buffer, RT)
- Forms very stable Cu(II) complexes

What are the optimal properties for a therapeutic radionuclide?

- β^- (or α) emitter
- What is the "optimal" β^- energy?
- No/minimal extraneous emissions
- Half-life?
- Imagable gamma?
- Cost/availability

Therapy: ^{67}Cu vs. ^{177}Lu

^{67}Cu

- $T_{1/2}$ = 2.6 d
- β^- Yield: 100%
- β^-_{mean} = 141 keV
- β^- range: 0.7 mm
- Gamma: 91 keV (7%), 93 keV (16%), 185 keV (49%)
- Production:
  - ^{68}Zn(p,2p)^{67}Cu (1.9 TBq/mg)
  - ^{68}Zn(γ,p)^{67}Cu (15 TBq/mg)

^{177}Lu

- $T_{1/2}$ = 6.6 d
- β^- Yield: 100%
- β^-_{mean} = 134 keV
- β^- range: 0.7 mm
- Gammas: 123 keV (6%), 208 keV (10%)
- Production:
  - ^{176}Lu(n,γ)^{177}Lu (1.1 TBq/mg)
  - ^{176}Yb(n,γ)^{177}Yb, ^{177}Yb → ^{177}Lu + β^- (3 TBq/mg)

Neuroblastoma Peptide Radiotherapy?

1. Does $^{64/67}$Cu-SARTATE accumulate in NB liver metastases?
2. Is treatment with ^{67}Cu-SARTATE as effective as treatment with ^{177}Lu-DOTATATE?
3. If we treat the disease early enough, can we prevent the development of metastases?
   - Prophylactic Radiotherapy

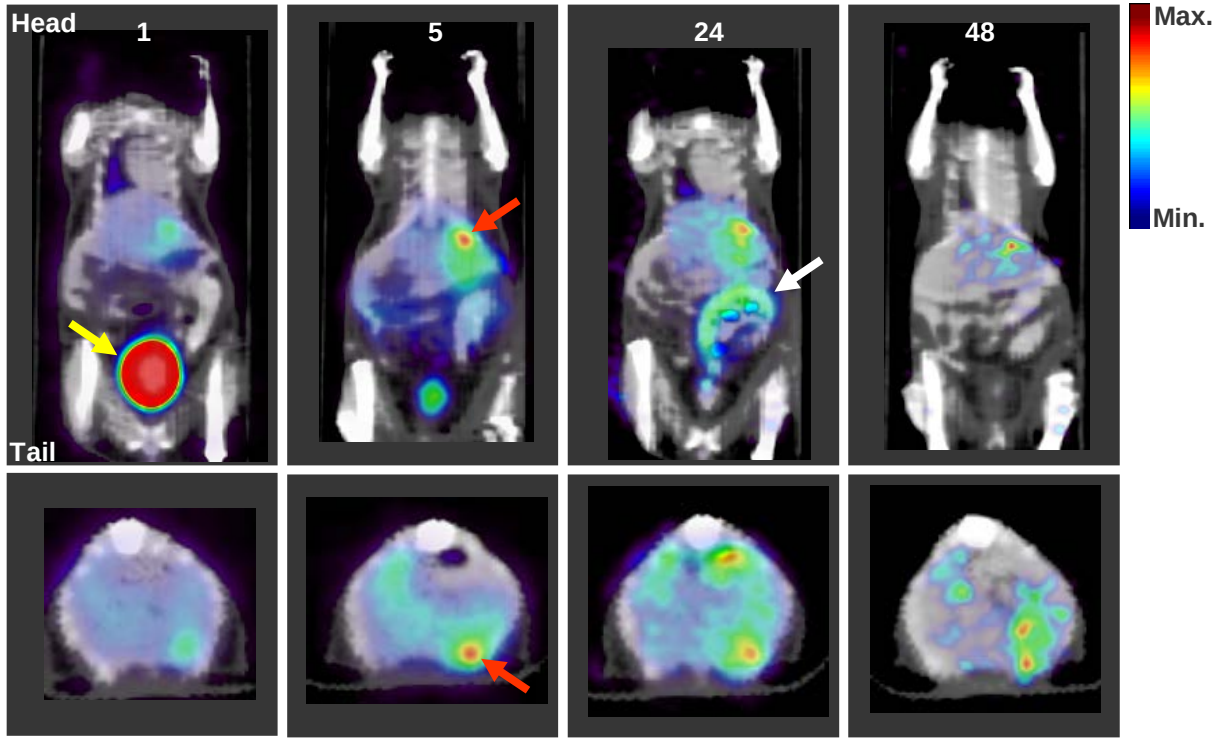
Animal model of disseminated liver mets

- Dorsal incision – Expose the spleen
- Inject 10^6 IMR32 (human) NB tumor cells
- Wait 2 min.
- Perform splenectomy
- Close incision
- 1-2 mm mets are present ~2 weeks after inoculation

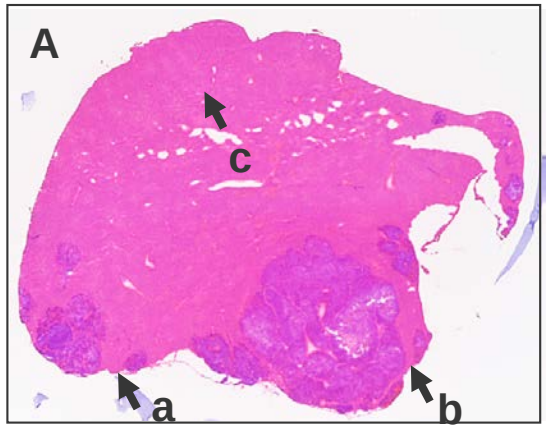
Animal Model: MicroPET Imaging

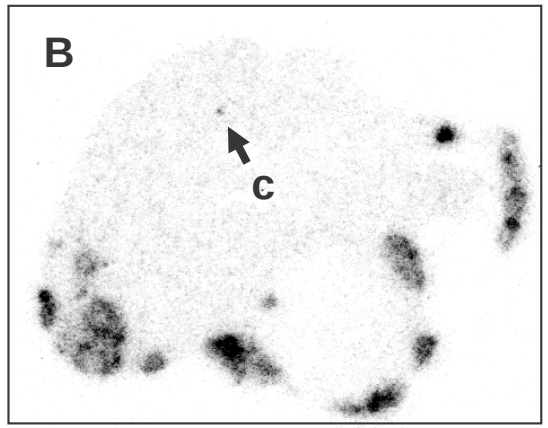
Imaging with ^{64}Cu-SARTATE

- Validate that the tumors have become established
- 3 weeks post-inoculation



Autoradiography and histology



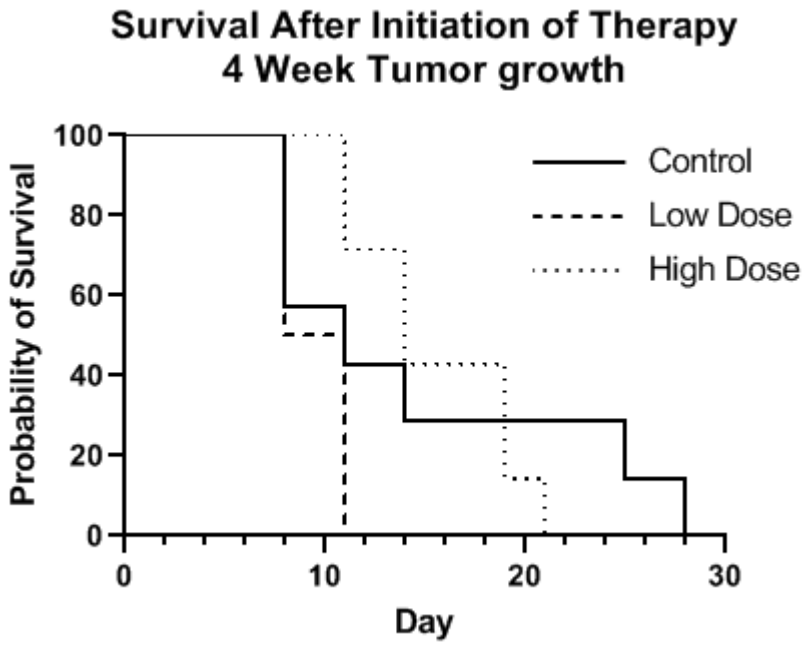


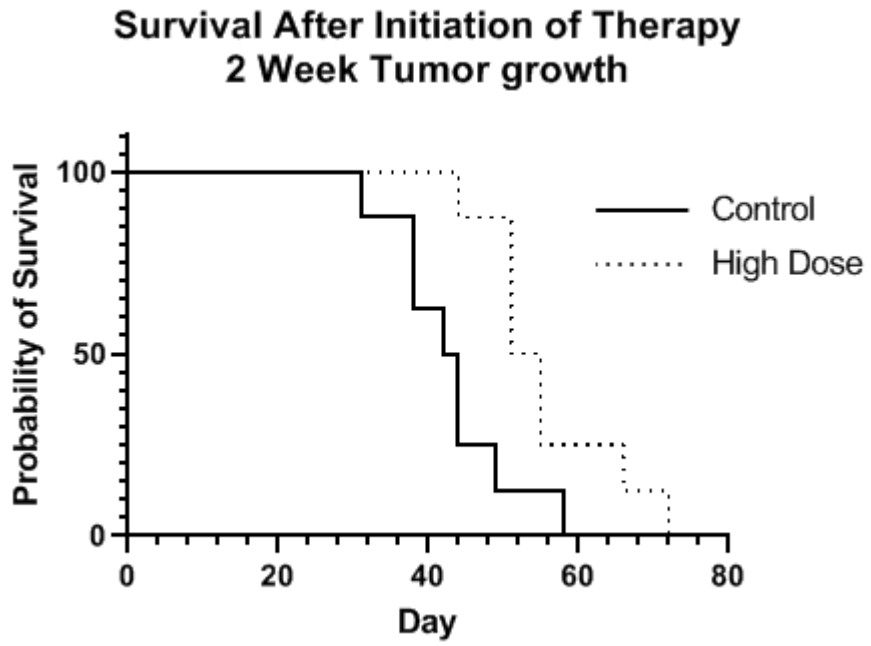
Animal Model: Therapy

Therapy

- Treat with ^{67}Cu-SARTATE
- Single treatment
- 4 weeks post-inoculation
  - Two different doses
    - 9.35 MBq (250 µCi)
    - 18.5 MBq (500 µCi)
- 2 weeks post-inoculation
  - Single dose (18.5 MBq)

^{67}Cu-SARTATATE – Therapy





	4-Week Incubation			2-Week Incubation	
^{67}Cu-SARTATE Dose	0 MBq (Control)	9.25 MBq	18.5 MBq	0 MBq (Control)	18.5 MBq
Mean Survival (d)	14.6±8.5	9.5±1.6	15.6±4.0	43.0±8.1	55.6±9.1
		p = 0.064		p = 0.012	

Dearling, et al., *EJNMMI Res* **11,** 20 (2021).

Conclusions and Questions

Conclusions

- Can image small (<1 mm) liver mets with ^{64}Cu-SARTATE
- ^{67}Cu-SARTATE extends life in mice with smaller tumors (2 weeks)
- ^{67}Cu-SARTATE is more effective for treating smaller tumors (2 weeks) than larger tumors (4 weeks)

Questions

- What about ^{177}Lu-DOTATATE vs. ^{67}Cu-SARTATE in metastases?
- Are higher doses of ^{67}Cu-SARTATE even more effective in the smaller tumors?
- Are α emitters more effective than β^- emitters for these very small lesions?
- Are antibodies better vectors than peptides?
- Is treatment more effective if started earlier, with smaller tumors?
  - Can we prevent the growth of mets? (prophylactic radionuclide therapy)

Acknowledgments

Intellectual

- Jason LJ Dearling, PhD

Financial

- Clarity Pharmaceuticals
- Children's Hospital Radiology Foundation

Thank you for your attention!