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Development of a novel hydroxyl dendrimer SPECT tracer, ^{111}In-D6-B483, for selective imaging of brain tumors

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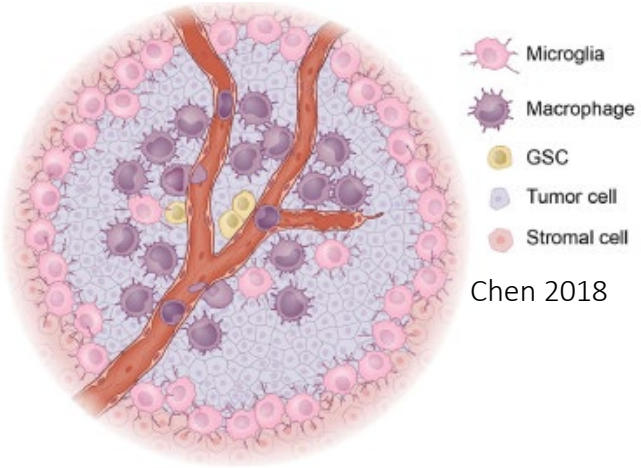
Neuro-Oncology Imaging & Radiotherapy Challenges

- Inability of radiotracers to cross blood brain barrier (BBB)
- Lack of specificity for only tumor tissue compared to normal tissue in brain
- Variable expression of radiotracer target across patients and tumor types
- Inability to image and treat brain metastases at early stage (single met) without false positives
- Radiation fraction in the brain tumor for radiotherapy insufficient to reduce tumor burden

Glioblastoma



Chen 2018

Reactive Microglia & Macrophage

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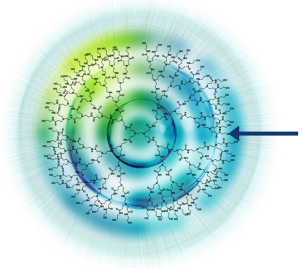
Disease Cell-targeted Precision Medicine

PROPRIETARY PLATFORM

Hydroxyl Dendrimer (HD)

< ½ size of antibody



Water-like surface

- Selective uptake: disease cell-targeted
- Systemic delivery with local sustained effect
- Crosses tissue barriers

Optimal for Intracellular Targets

MULTIPLE THERAPEUTIC AREAS

NEUROLOGY

OPHTHALMOLOGY

NEURO-ONCOLOGY

Crossing tissue barriers: (blood/brain or blood/retinal)

7 Animal Species + Human Data

CLINICAL STAGE

OP-101:
2 Phase 1 Studies (HV)
Phase 2 Study (COVID)
Well-tolerated

OP-801:
IND in Q4 ’21 (ALS)

D-4517.2:
Phase 1 (HV) in Q4 ’21

Crosses Tissue Barriers and Selective Uptake by Reactive Microglia & Macrophages

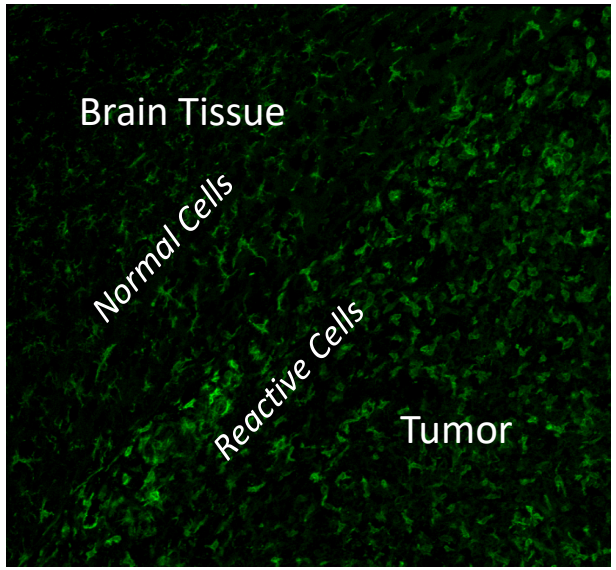
Selective: HDT Uptake Only in Reactive Cells

TUMOR ASSOCIATED MACROPHAGES

Glioblastoma Orthotopic Tumor Model In Rat

ANTIBODY

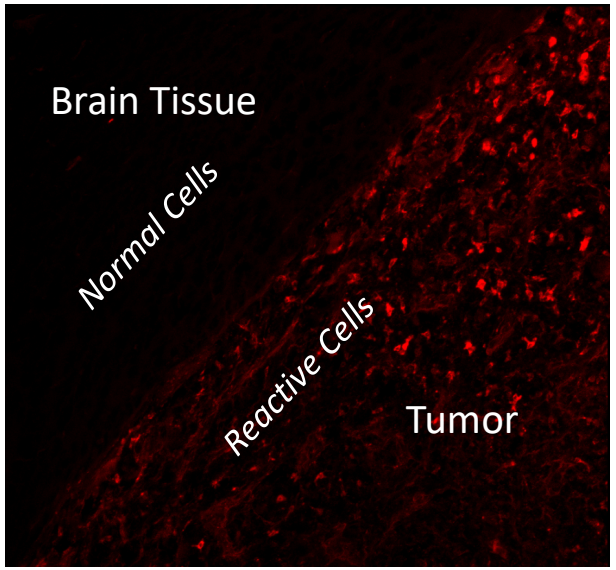
Iba1: Macrophages/Microglia



Labels ALL CELLS

HYDROXYL DENDRIMER

Single Intravenous injection of HD-Cy5



Only labels REACTIVE CELLS

Lack of off-target toxicity

Cleland 2020; Liaw 2020; Zhang 2015

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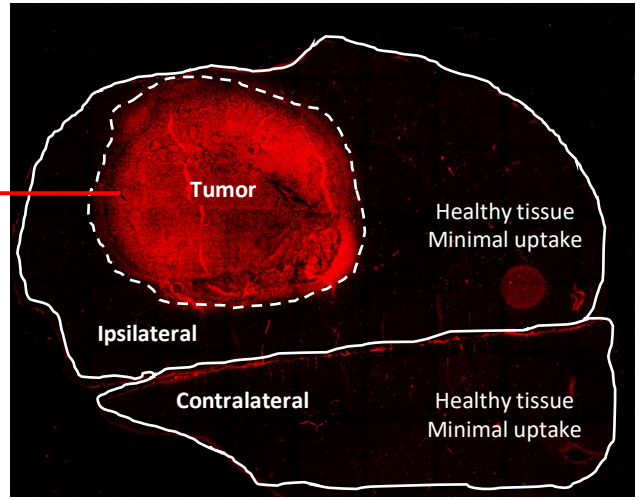
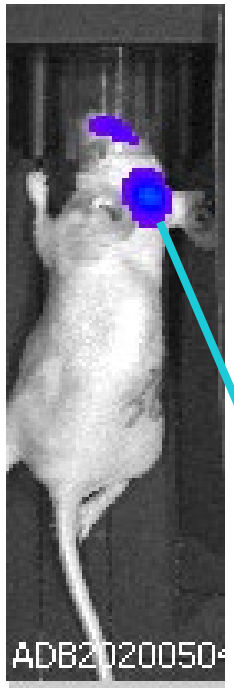
Selective Uptake By Tumor Associated Microglia and Macrophages

BRAIN TUMORS
(Glioblastoma Model in Rat)

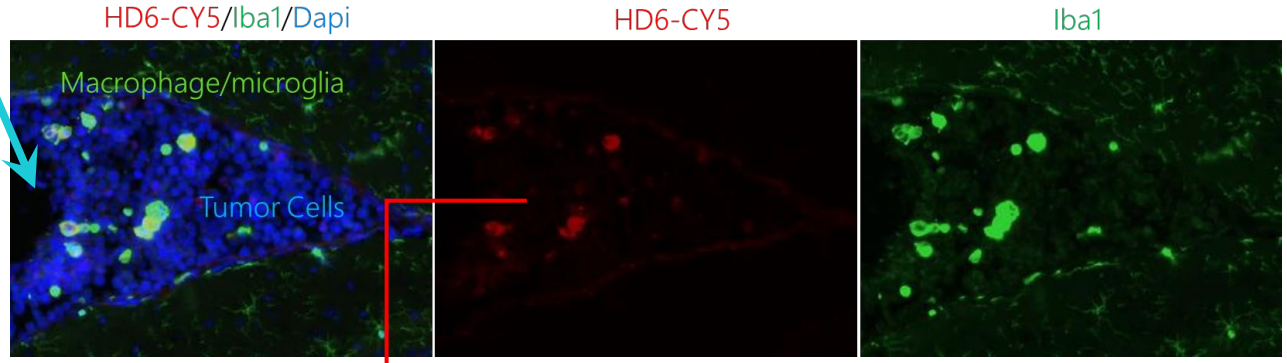


Liaw 2019



BRAIN METASTASES
(Mouse Model)

Brain Metastases from IV Molt4-luc Cells
Single IV dose of HD-Cy5



HD (in red) crosses blood brain barrier and is taken up by reactive inflammatory cells (TAMs)

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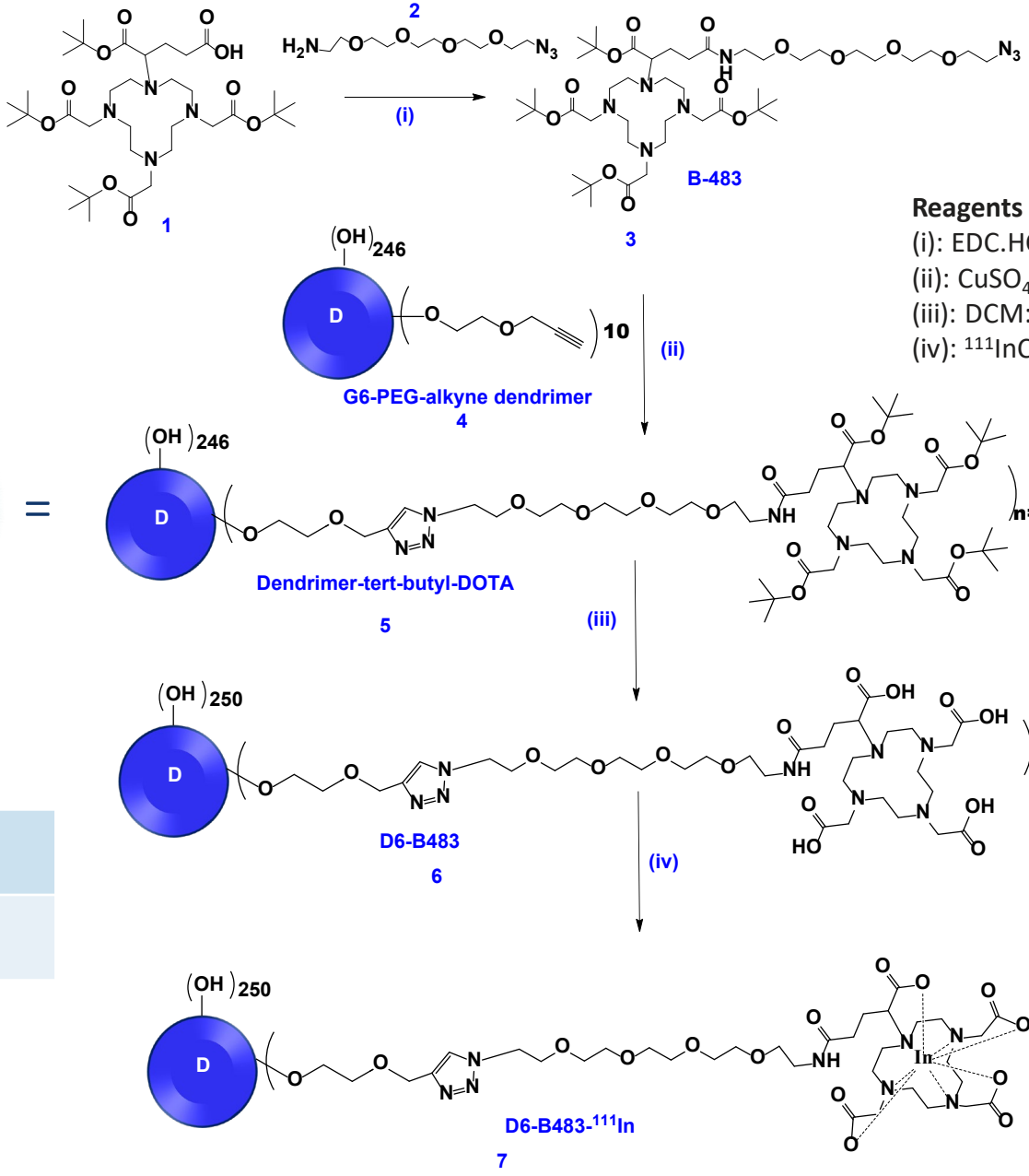
Synthesis of D6-B483



Reagents & Conditions:
(i): EDC.HCl, HOBt, DIPEA, DMF, RT, overnight
(ii): $CuSO_4.5H_2O$, Na ascorbate, DMAc:H_2O, 8h
(iii): DCM:TFA (1:1)
(iv): $^{111}InCl3$, Sodium acetate, pH5.5, 70°C

Labeling Efficiency	73%
Radiochemical purity	96%

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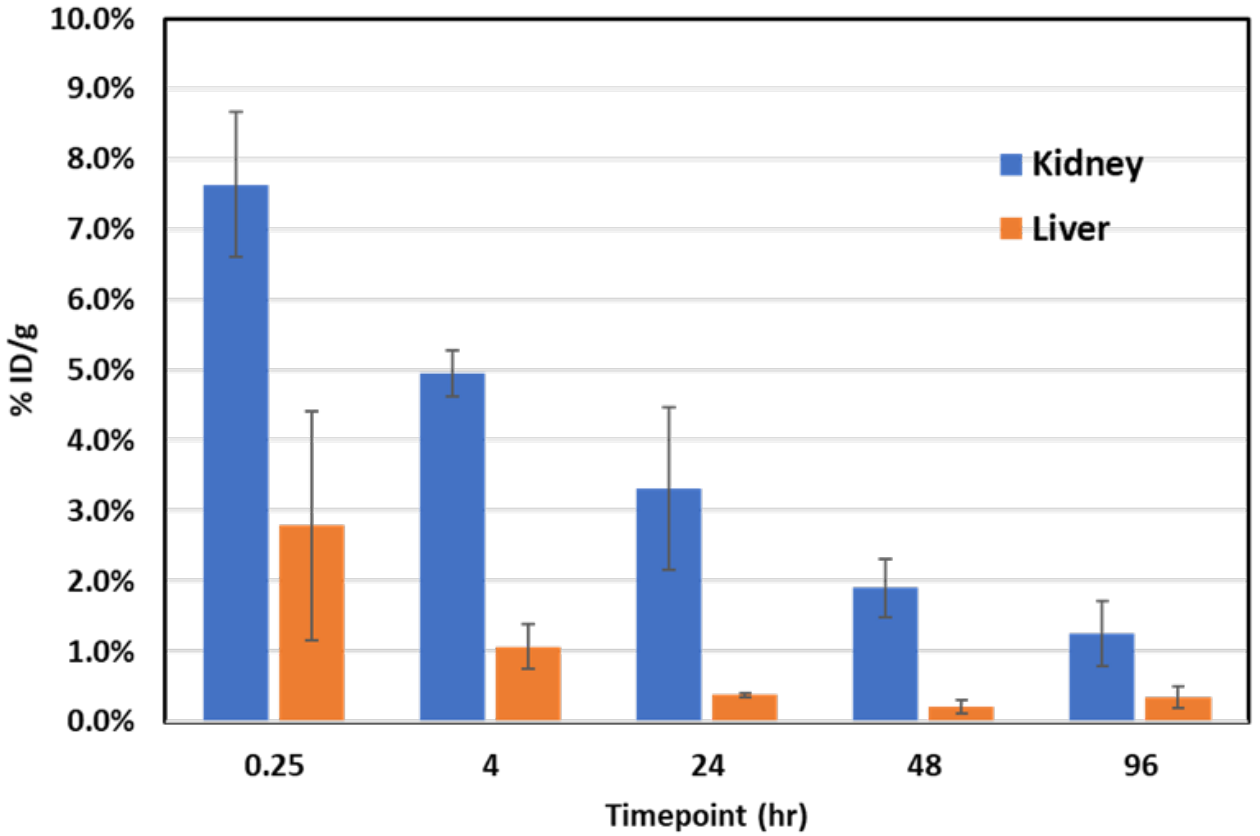
Distribution of D6-B483

- Cy5 labelled D6-B483 with either 2-3 or 8-10 DOTA (10 mg/kg) was administered IV to mice.
- Mice (3/timepoint) were sacrificed at 15 min, 4, 24, 48, and 96 h post-dose.
- Amount of Cy5-D6-B483 was measured in kidney and liver after tissue homogenization and extraction.

Liaw 2020; Lesniak 2013



Rapid Renal Clearance

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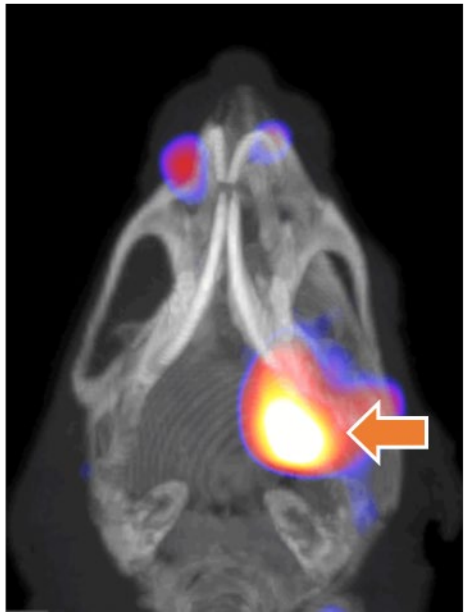
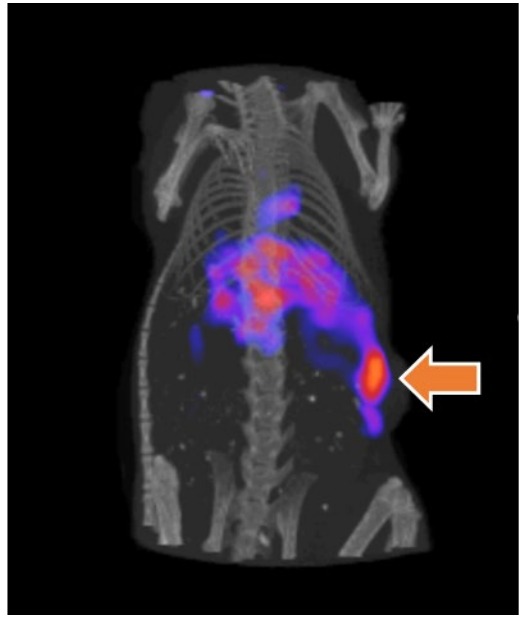
Evaluation of Selective Uptake In Brain and Solid Tumors

- 20 mice implanted with 10^6 GL-261-luc2 cells by stereotactic intracranial (IC) surgery
- Brain tumor size and location by bioluminescence (BLI) to confirm tumor sizes (MRI to BLI correlations previously established by Invicro)
- 8 mice implanted subcutaneous (SC) with 10^6 GL-261-luc2 cells; Dosed once tumors were between 125 to 350 mm^3 (caliper measurements)
- IV dose of ^{111}In-D6-B483 (~230 µCi, 45 µg)
- SPECT/CT images: 3-6, 24, 48, 72 and 96 h post-dose

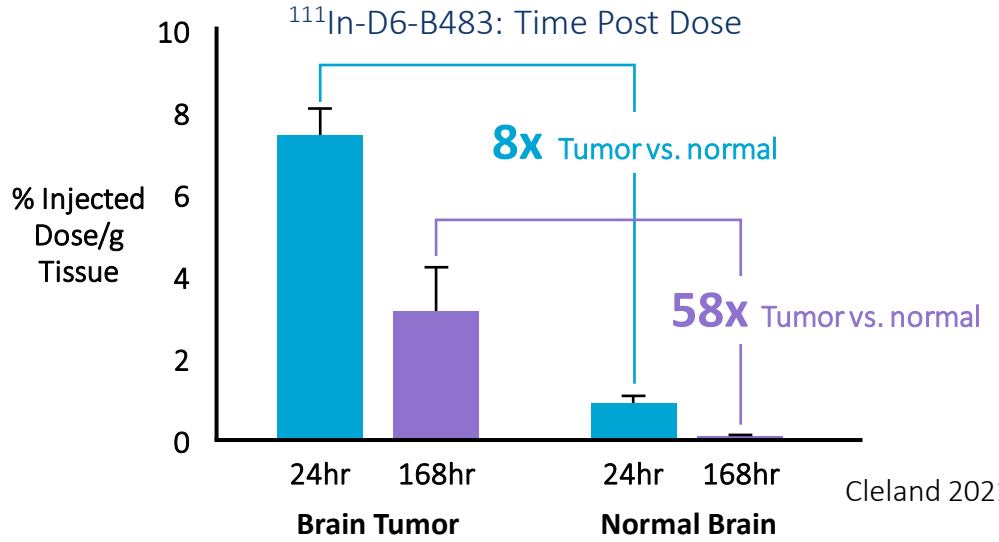
Intracranial (IC)



Subcutaneous (SC)



Previous Study Demonstrating Persistence



Cleland 2021

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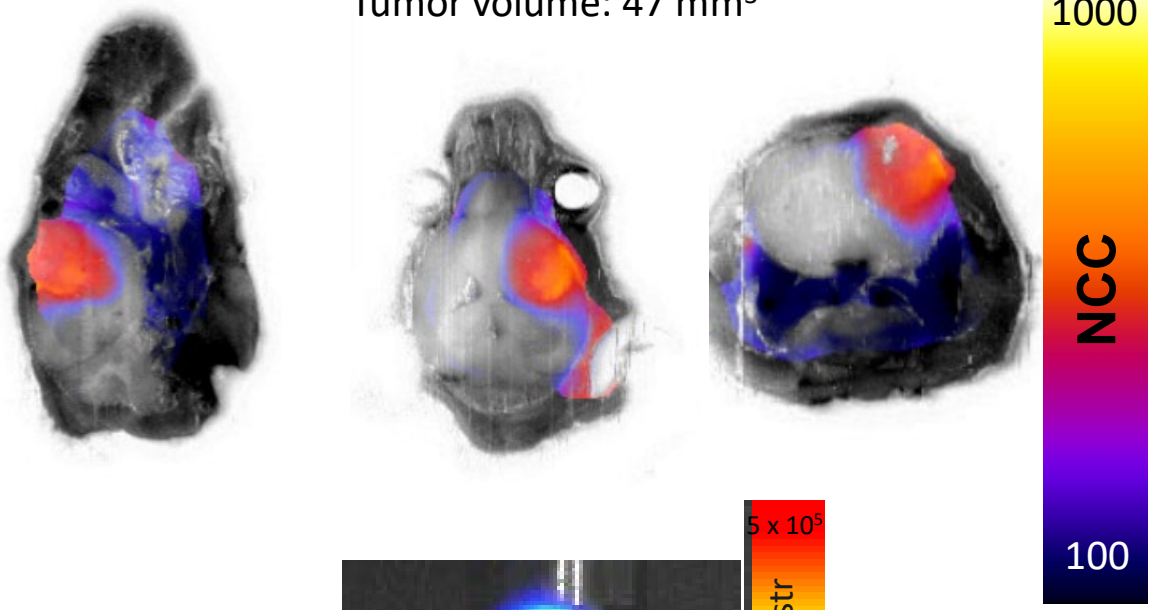
Localization of D6-B483 in Large Tumors

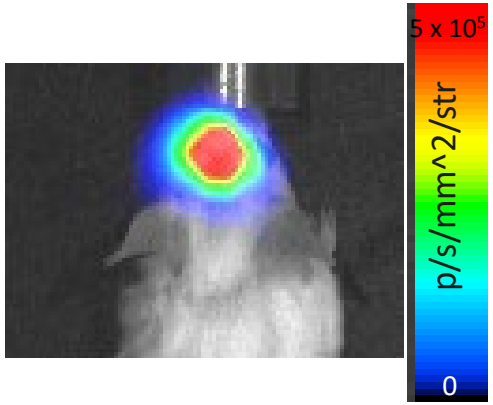
Cryo-fluorescence Tomography (CFT)
Cy5-D6-B483

Subject 6, Hour 48

Tumor volume: 47 mm^3



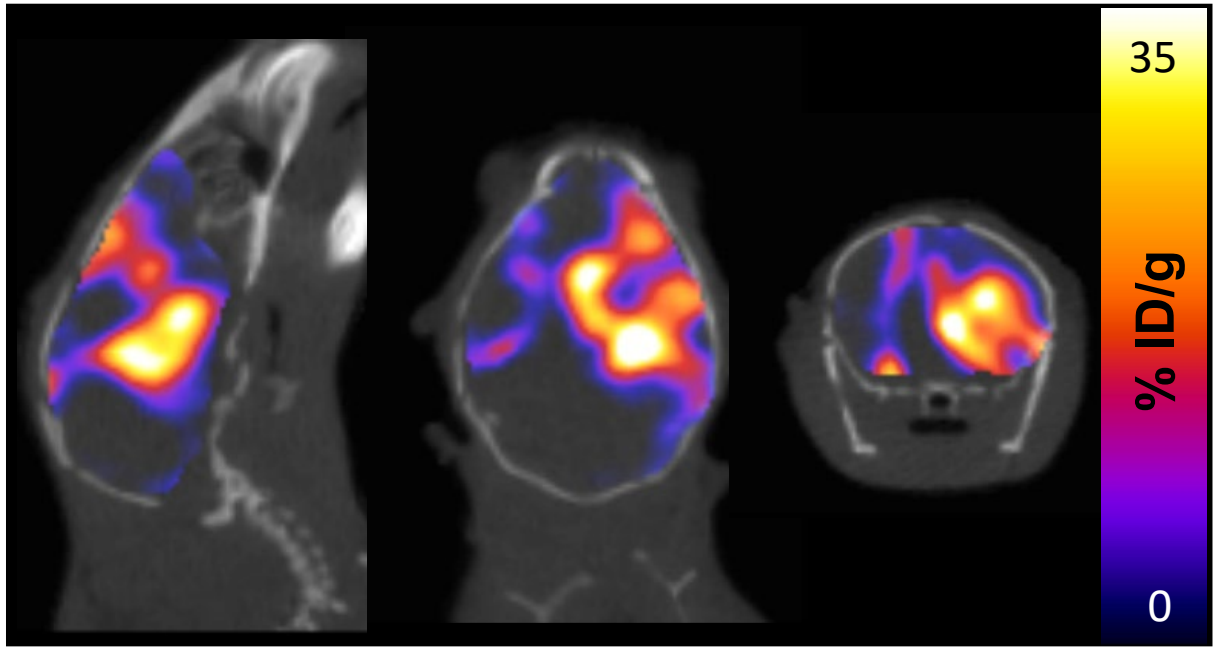
BLI



SPECT/CT
^{111}In-D6-B483

Subject 1, Hour 48

Tumor volume: 61 mm^3



Tumor/Contralateral Ratio = 8

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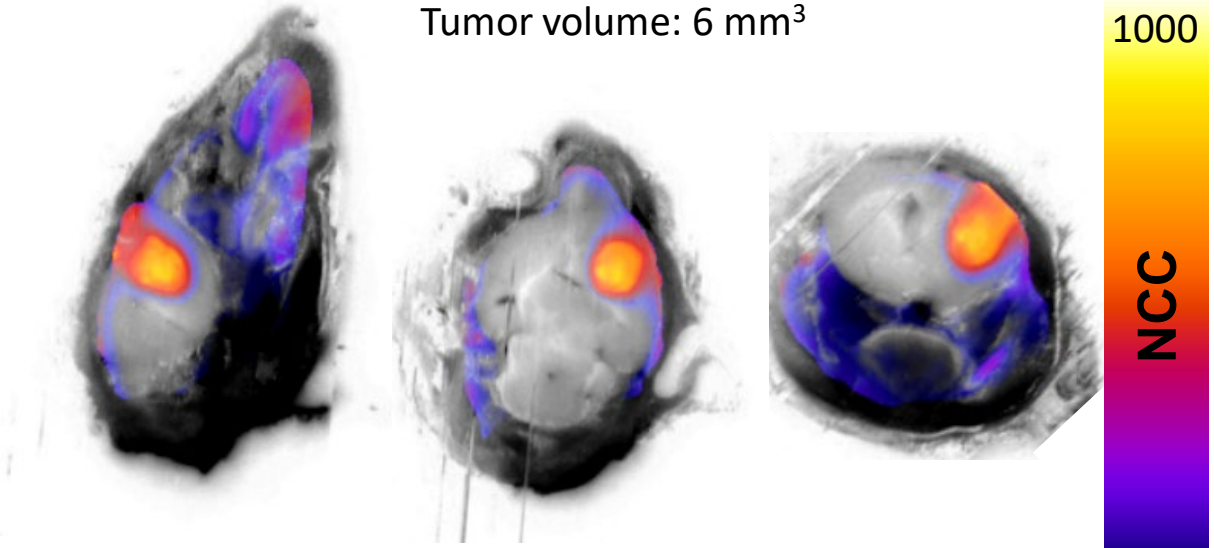
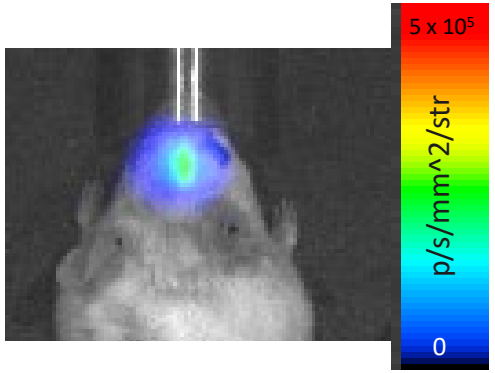
Localization of D6-B483 in Small Tumors

Cryo-fluorescence Tomography (CFT)
Cy5-D6-B483

Subject 18, Hour 48
Tumor volume: 6 mm^3

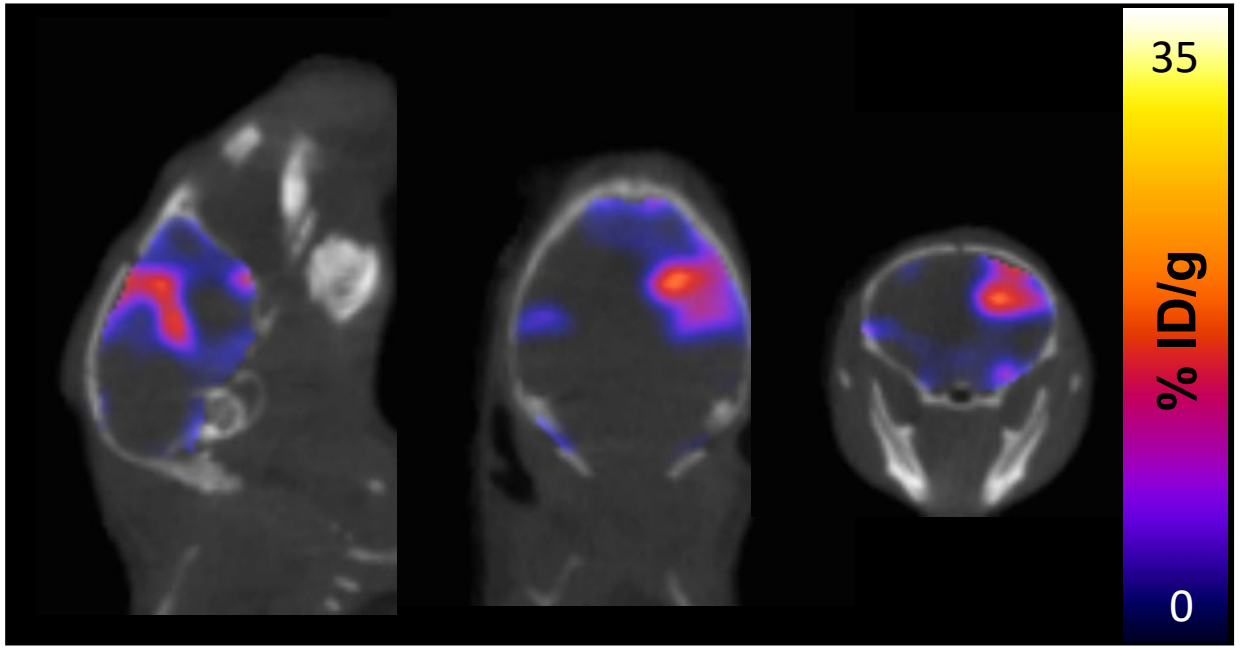


BLI



SPECT/CT
^{111}In-D6-B483

Subject 4, Hour 48
Tumor volume: 9 mm^3



High Sensitivity to Detect Small Tumors

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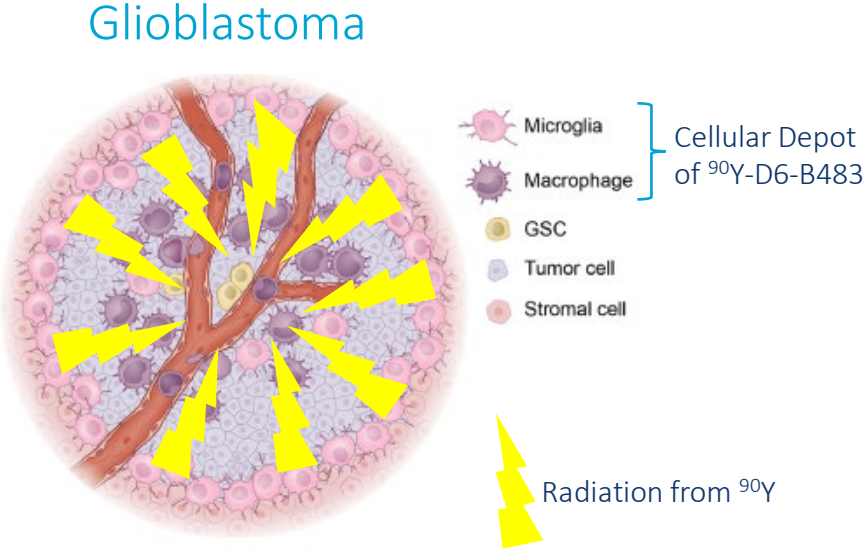
Radiotherapy Plan

- Choice of Radioisotope
  - Long pathlength to kill adjacent tumor cells
  - Long isotope half-life to avoid need for repeat dosing
  - Selected Isotope: ^{90}Y – 2.7 day half-life, 4-5 mm pathlength

- D6-B483 Persists in TAMs for up to 1 month
  - Local cellular depot of radiation
  - Minimize systemic exposure (cleared in 48 h)

- Planned Studies
  - Orthotopic GBM mouse model
  - Metastatic melanoma mouse model (^{111}In followed by ^{90}Y)



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Overview of Clinical Strategy for Brain Cancer

POC of Tumor Targeting Across BBB
Leverage to Select Patients for HD Therapeutics (HDTs)

^{111}In-D-B483 Phase 1 → ^{90}Y-D-B483 Phase 1

Patients with GBM & Brain Mets

HDT Doses Matched to Uptake (within range)
to Maximize Effect on Tumor

Select & Stratify Based
on SPECT/CT Quantification → HDT Phase 1/2

^{111}In-D6-B483
Screening

Patients with GBM & Brain Mets

(HDT consists of SAME D6 used for Imaging = Same Distribution)

Pre-IND for ^{111}In-D6-B483 Submitted to FDA – Feedback Expected by Nov 2021

Ability to Detect & Treat Brain Metastases