AACR VIRTUAL SPECIAL CONFERENCE
RADIATION SCIENCE AND MEDICINE
March 2-3, 2021

Selective Targeting and Imaging of Orthotopic Glioblastoma after a Single Systemic Dose of a Novel Hydroxyl Dendrimer Radionuclide

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Ashvattha THERAPEUTICS

Disclosure Information

Jeffrey L Cleland, PhD

I have the following financial relationships to disclose:

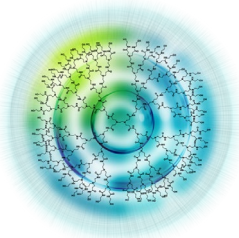
Stockholder in: Ashvattha Therapeutics

Employee of: Ashvattha Therapeutics

I will not discuss off label use and/or investigational use in my presentation.

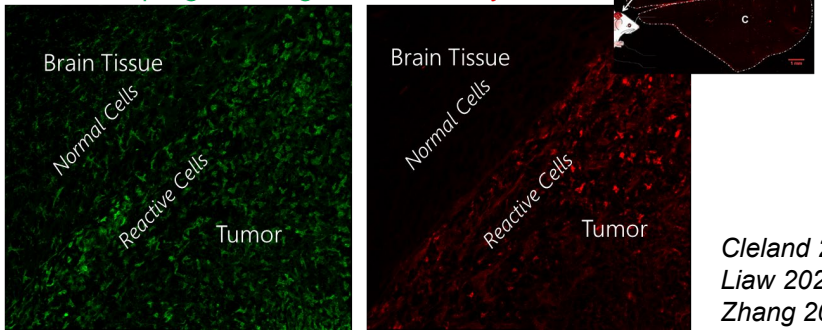
Hydroxyl Dendrimers Cross BBB & Target TAMs

Hydroxyl Dendrimer (HD)



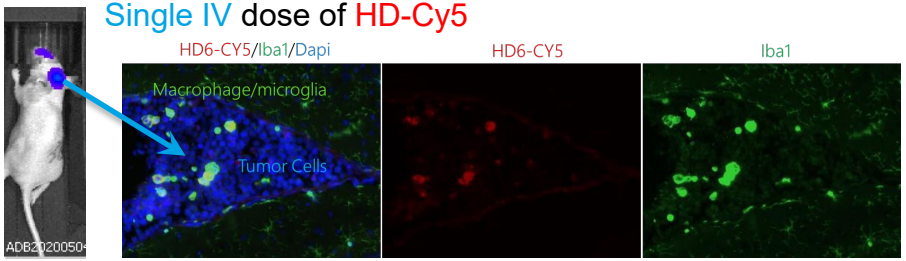
- *< ½ size of antibody*
- Water-like Surface (novel finding)
- Targets Key Cells, No Ligand Needed
- Crosses BBB in presence of inflammation
- Only taken up by reactive inflammatory cells in diseased tissues (broad range of diseases)
- No uptake in peripheral macrophages or Kupfer cells
- Renal clearance in animals & humans
- >85 published studies, 7 species, >30 animal models

Orthotopic Glioma in Mice
Single IV dose of HD-Cy5



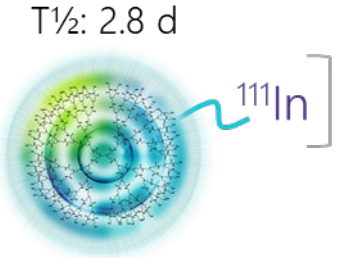
Cleland 2020
Liaw 2020
Zhang 2015

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



Imaging Study Design

- HD Constructs
  - HD4 and HD6 (~4 or 6 nm diameter)
  - DOTA covalently linked to HD via linker arm conjugated to hydroxyl on HD surface
  - ^{111}In radiolabeling with >95% radiochemical purity

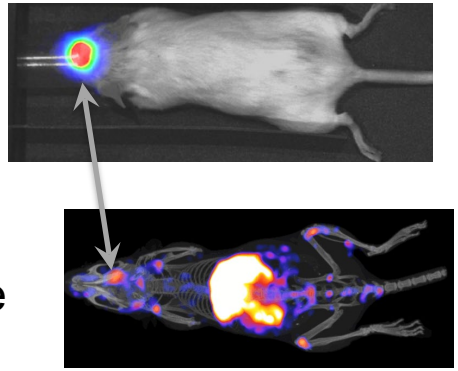


- Animal Model
  - GL-261-luc orthotopic glioblastoma mouse model
  - Tumor implant followed by monitoring with bioluminescence
  - Single IV dose of HD4-DOTA-^{111}In or HD6-DOTA-^{111}In at 0.5 mg/mouse or 0.3 mCi/mouse (3 mice per group)
  - Whole body SPECT/CT imaging up to 7 days post-dose
  - Quantitative biodistribution and uptake using VivoQuant 4.0

Tumors & Biodistribution

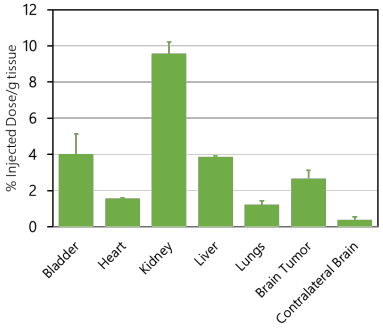
- Tumor volumes from bioluminescence
  - HD4 Group: 15, 24, & 43 mm^3
  - HD6 Group: 14, 26 & 38 mm^3
- Biodistribution
  - Clearance through kidney into bladder/urine

Subject 7: 14 mm^3 tumor

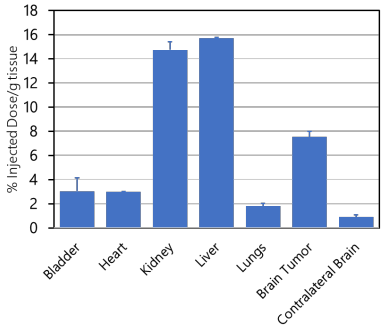


Subject 7: HD6-DOTA-^{111}In 24 h

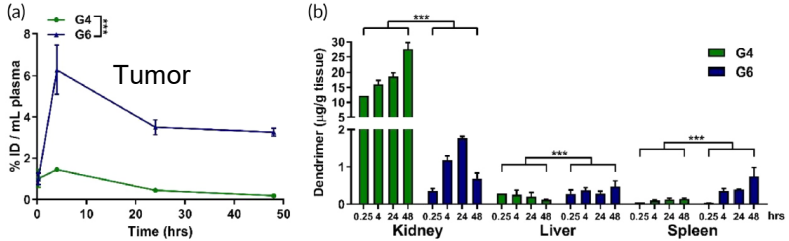
HD4 – 24 h



HD6 – 24 h



Previous Study (Orthotopic GBM)

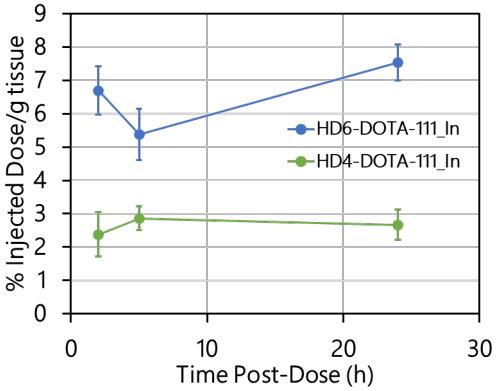


HD4 or HD6 with Cy5 Label

Liaw 2020

Selective Brain Tumor Targeting

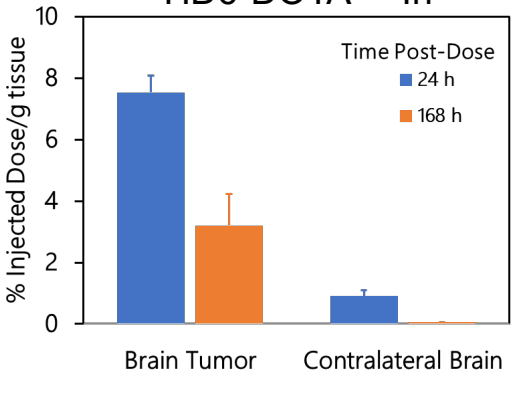
Rapid Tumor Uptake



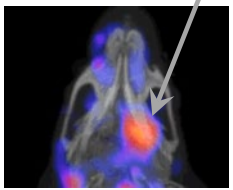
HD6 Uptake > HD4 Uptake

Selective & Persistent

HD6-DOTA-^{111}In

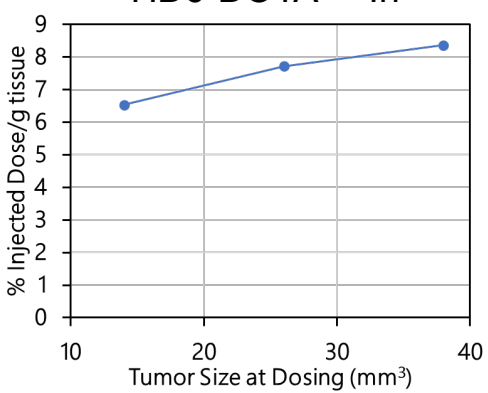


24 h: 8x tumor/normal
168 h: 58x tumor/normal
(7 days)



Tumor Size Impact

HD6-DOTA-^{111}In



Summary & Next Steps

- HD6-DOTA-^{111}In is selectively taken up and persists (>7 d) in brain tumors yielding high signal relative to normal brain tissue
- HD4 and HD6 are primarily cleared via kidneys (urinary excretion)
- This study demonstrates the potential to use HD6 to target and image brain tumors and brain metastases
- HD6-DOTA construct optimization ongoing
- HD6-DOTA-^{90}Y in orthotopic GBM mouse model and dosimetry studies planned
- HD6-DOTA-^{111}In IND in Q4 to assess imaging of patients with brain tumors and brain metastases