NeuroSn, Inc.

LOCALIZING APOPTOSIS-INDUCING SN-117M TO BRAIN NEUROINFLAMMATORY CELLS

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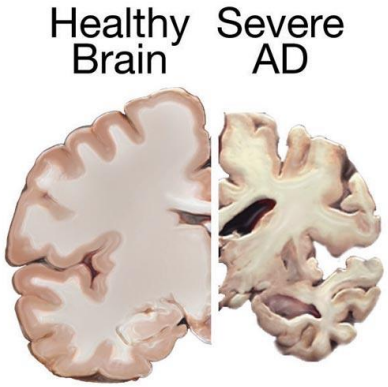
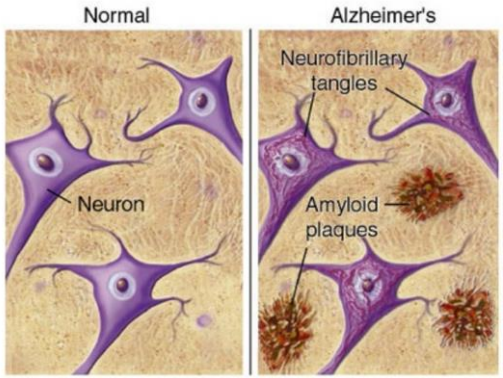
What is Alzheimer's Disease

- Alzheimer's disease (AD) is:
  - An **irreversible, progressive brain disorder**
  - Slowly destroys memory and thinking skills
  - Eventually, the ability to carry out the simplest tasks
  - In most people symptoms first appear in their mid-60s
  - It is the most common cause of dementia among older adults

- AD patients usually have **abnormal plaques and tangles** as well as loss of connections between neurons in the brain





Alzheimer's Disease/Microglia Background

- **Amyloid Cascade Hypothesis**
  - A current therapy development approach with many **failed therapeutic trials**
  - It may be that "Amyloid is the tombstone", i.e., a marker of disease
- **Neuroinflammatory Hypothesis**
  - CNS **microglia are part of the inflammatory pathway** to Aβ formation and to accumulation of tau protein is a major hallmark of AD
  - Depleting microglia dramatically suppresses propagation of tau protein
- Induction of microglia apoptosis is not currently a direction by industry
  - **Target 'aged' macrophages/microglia**
- Delivery of a Sn-117m targeting molecule to human brain has been validated in a human dosimetric study
  - Sn-117m has been shown to be safe and it can deliver conversion electron energy to **induce apoptosis in peripheral macrophages in several inflammatory conditions** (slide 8)

Aim: To develop Sn-117m carrying molecules that target the sites of neuroinflammation in AD

To induce apoptosis in microglia and CNS macrophages that induce the cascade of events that produce Aβ formation and the propagation of tau

- **Apoptosis** – "A form of cell death in which a programmed sequence of events leads to the elimination of cells without releasing harmful substances into the surrounding area"
- Sn-117m is being linked to targeting agents to localize to inflammatory pathways and to induce apoptosis
- NeuroSn, Inc. is affiliated with other companies that have extensive background in the **reduction of inflammation** using Sn-117m targeting compounds
- Delivery of a **Sn-117m linked targeting agent** to the brain in humans has been achieved using Sn-117m-DOTA-annexin V (slide 8)

Targeting CNS Inflammatory Cells Involved in Neurodegeneration

Anchoring conversion electron (CE) emitting Sn-117m to inflammatory cells and affected neurons in AD and other neuroinflammatory diseases

<u>Sn-117m linked targeting agents</u>

Already developed:

- **Sn-117m-DOTA-annexin V** – Used in inflammatory states in animal models and in humans
- **Sn-117m-DOTA-lipocortin (annexin A1)** – molecule produced

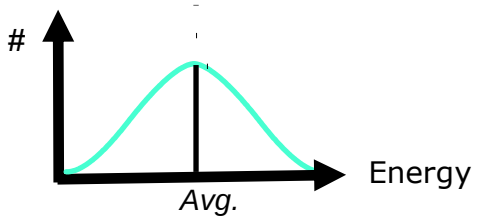
In development:

- **Sn-117m-DOTA+8 amino acid peptide** – molecule produced and ready for AD model testing

CNS localization to inhibit the neuroinflammatory cascade of (1) β amyloid (plaques) and (2) hyperphosphorylation of microtubule-associated tau neurofibrillary tangles

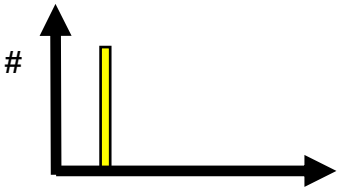
Characteristics of Sn-117m

Beta Particles

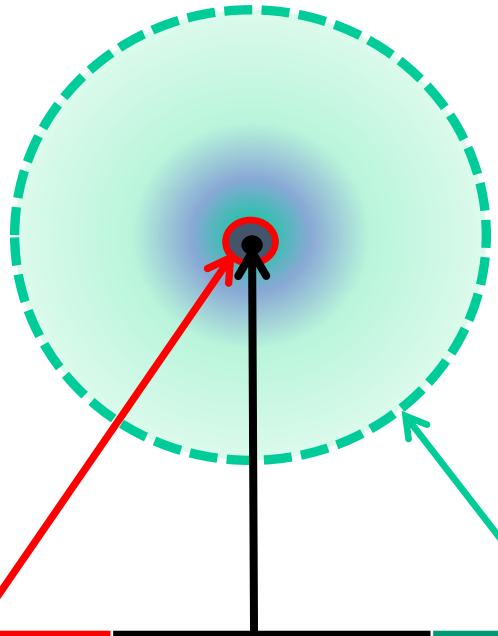


Produces a *range* of tissue penetration

Conversion Electron (CE)



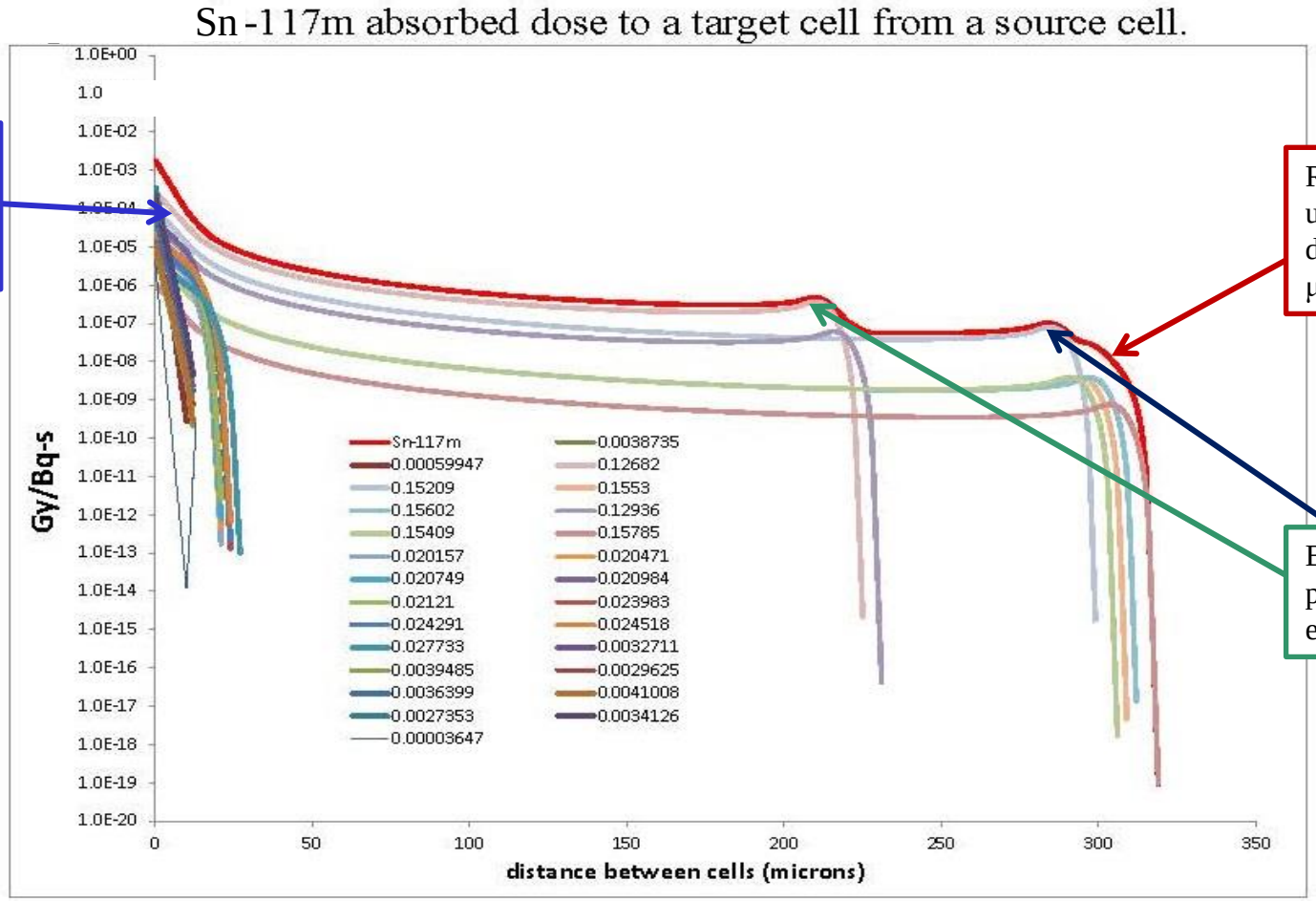
Penetrates up to a *set distance* (discrete energy)



	Sn-117m (CE)	Alpha Particles[1]	Beta Particles[2]
Range in tissue (µm)	300	40-90	50-5000
Shielding needed during administration	No	No	Yes

[1]XOFIGO; [2]METASTRON & QUADRAMET

Well-defined Range of Sn-117m in Tissue



Short-range dose boost from Auger electrons

Relatively uniform total dose over 300 µm tissue depth

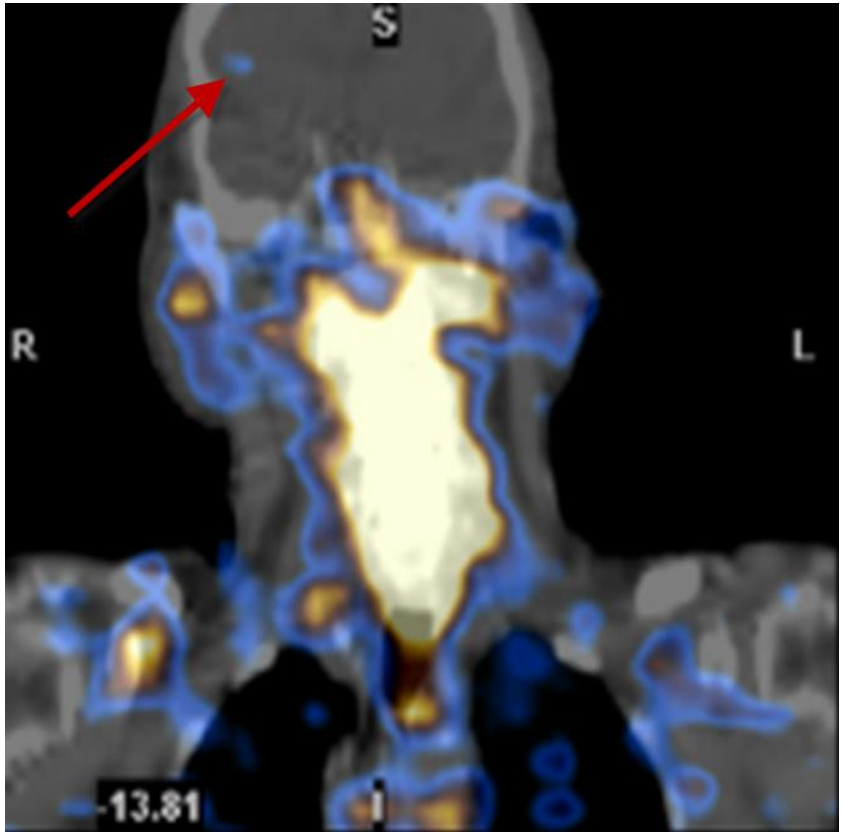
Bragg peaks (end points) for higher energy C.E.

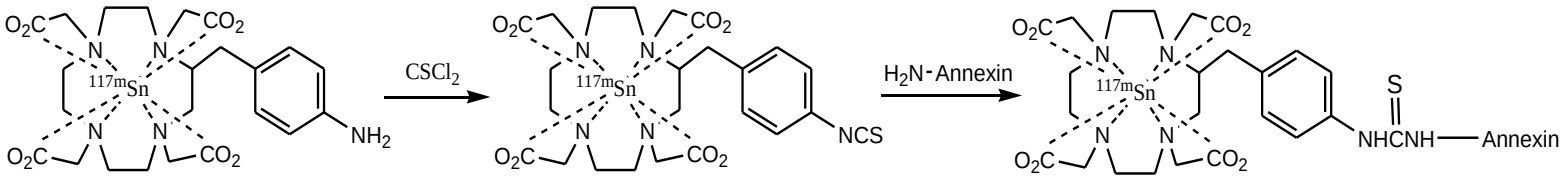
Sn-117m Targeting to CNS Inflammatory Cells

- **Microglia, the macrophages of the brain**,

  are a potential target for treatment based on the neuroinflammatory hypothesis of AD
- Annexin V binds to the outer leaflet of the cell

  membrane of cells undergoing apoptosis
- **Sn-annexin V** actively crosses the Blood Brain Barrier and **induces apoptosis in macrophages**
- Annexin A1 crosses and stabilizes/repairs the BBB, and is strongly expressed in AD
- Annexin A1 and annexin V are very similar in structure





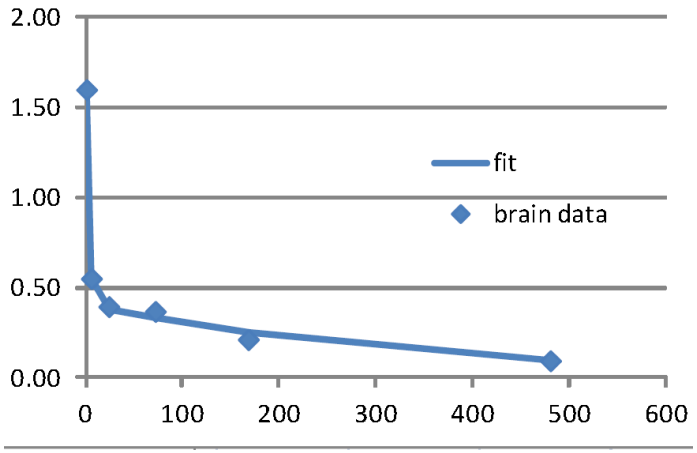
Sn-ABD Sn-IBD Sn-Annexin

NeuroSn Approach

Microglia are the target for systemically delivered Sn-annexin V that crosses the inflamed blood brain barrier (BBB) in patients with AD

- Sn-annexin V must enter and reside in the brain in order to induce apoptosis in aged microglia
- **Intravenous delivery of Sn-annexin V across the BBB** and into the human brain has already been validated in a human dosimetry study, i.e. we can use Sn-annexin V
- We are creating an **improved molecule using Sn-117m + 8 amino acid Aβ derivative**
- This molecule will be tested in a mouse model etc.

Dosimetry of Sn-annexin V in patients with injured BBB



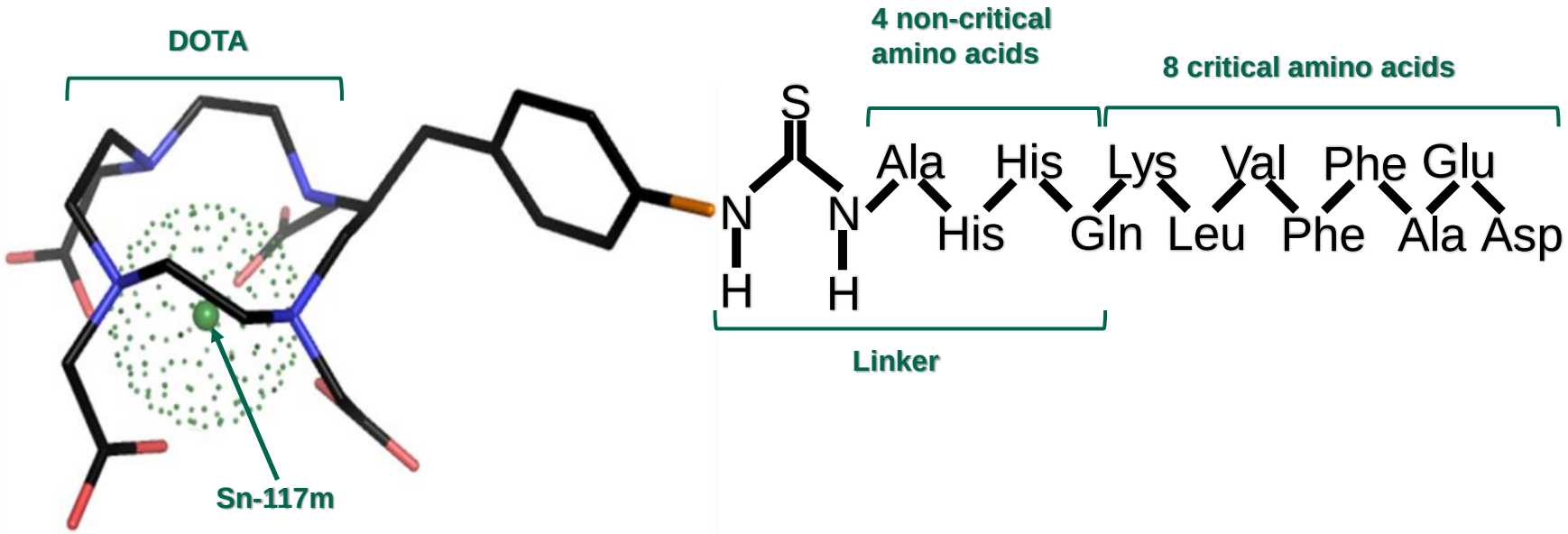
RAGE - Receptor Involved in Inflammatory Disorders

- The **r**eceptor for **a**dvanced **g**lycation **e**nd products (**RAGE**) is a **multiligand receptor involved in inflammatory disorders**, including AD
- Compelling evidence suggests that RAGE acts as an inflammatory **intermediary**
- A critical role of RAGE in AD includes beta-amyloid (Aβ) production and accumulation, the formation of neurofibrillary tangles, failure of synaptic transmission, and neuronal degeneration
- **Microglia in AD-affected regions have higher levels of RAGE** in the AD brains than that in the age-matched non-AD controls
- **RAGE could be a trigger for the pathogenesis of Aβ and tau** hyper-phosphorylation which both participate in the process of cognitive impairment; expression levels of RAGE are correlated to the severity of the disease
- Preclinical and clinical studies support RAGE inhibitors as potential therapy agents in AD and RAGE may be a novel **anchoring site for CE therapy**

RAGE Targeting

4-(DOTA-2-yl-methyl)-phenylcarbamothioyl-β-Ala-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-OH trifluoroacetate salt

A RAGE-targeting molecule containing a **critical 8 amino acid (aa) portion** plus Sn-117m linked DOTA has been constructed



Next Steps

- Cold Sn-117 and low specific activity (LSA) Sn-117m in **design** of Sn-117m-DOTA-8 amino acid **molecule yield and stability** is in process
- Peripheral high affinity of Aβ for itself – binding to Aβ 1-42 loculated in peripheral muscle with LSA and HSA Sn-DOTA-8AA
- **Safety** of systemically injected Sn-DOTA-8AA
- High specific activity (HSA) production of Sn-DOTA-8AA
- Use of HSA Sn-117m in the production of Sn-DOTA-8AA in animal brain **binding, dosimetry, imaging and retention**
- **Binding and localization** of LSA Sn-DOTA-8AA to V-RAGE in cells and animals
- **cGMP production** of Sn-117m-DOTA-8AA and preparation for **pre-human trials**