Amphipathic Oral Chelators and Radionuclide Contamination

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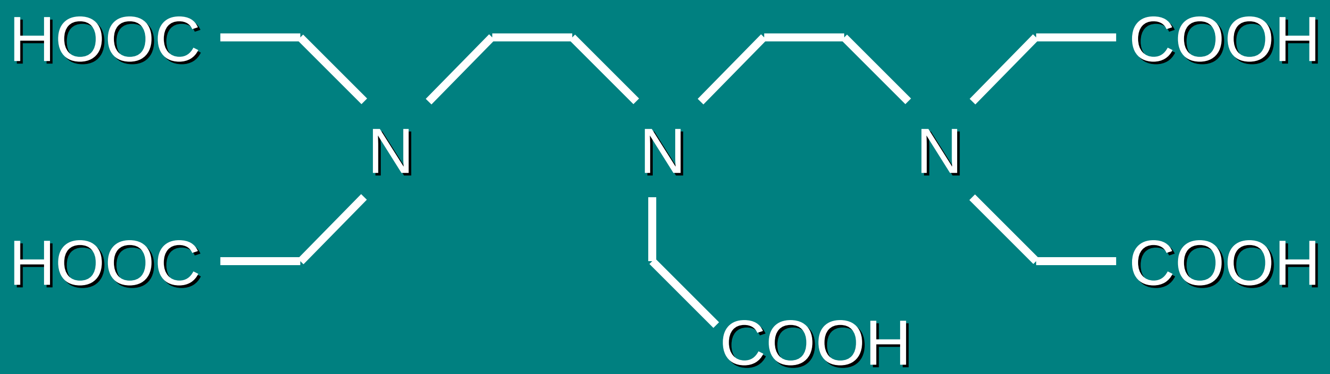
Overview

- Chelation objectives and chelator design
- Possible advantages/disadvantages
- Excretion pathways
- Detection methods
- Binding affinities
- Efficacy: Pu, Am, U, Co, others
- Safety
- Ongoing studies:

Chelator Design

- Orally active
- Polyaminocarboxylic acid family
- Effective for actinides (esp. Pu and Am)
- Broad efficacy for other metals
- Suitable for long-term use
- Low toxicity

DTPA



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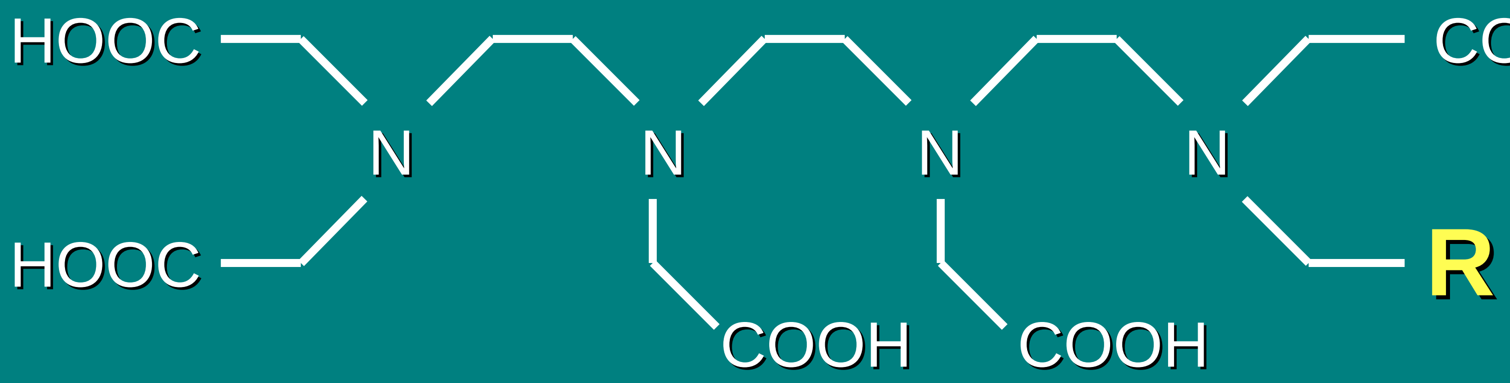
Amphipathic Triehylenetraminepentaacetic (TT) Chelators



R $= (CH_2)_6CH_3$

$= (CH_2)_{10}CH_3$

$= (CH_2)_{14}CH_3$

$= (CH_2)_{20}CH_3$

Amphipathic Polyaminocarboxylic Acid Chelators

Possible advantages?

- Orally available
- Better organ/tissue availability?
- Target organs?
- Select excretion pathways
- Different coordination than DTPA
- Safety
- Efficacy for Pu and Am

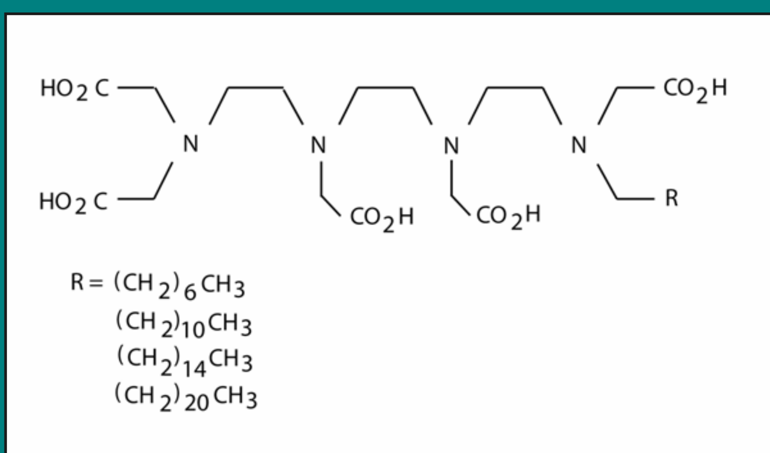
Possible disadvantages?

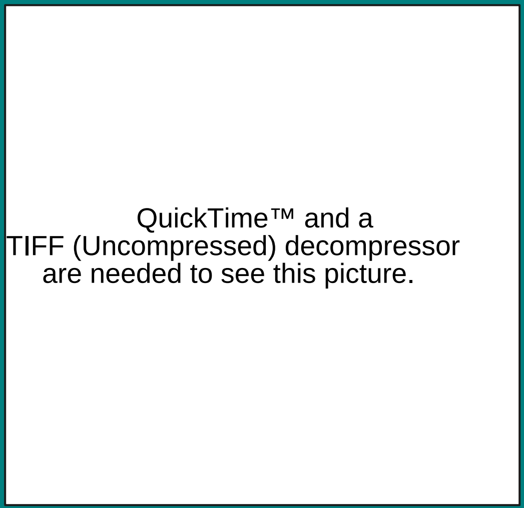
- Bind in tissues?
- Amphipathic - toxicity?
- Translocation?
- Slower acting?

Polyaminocarboxylic acids can bind a broad range of metals and radionuclides

Disadvantages: When exposure is from one well characterized nuclide.

Advantages: When exposure is to multiple metals/nuclides, or composition not well known





Amphipathic Properties and Excretion Pathways

Biliary Excretion

Liver

↓

Bile

↓

Feces

More Lipophilic
[C_{22}TT]

Less Lipophilic
[C_4TT]

Urinary Excretion

Blood

↓

Kidney

↓

Urine

Detection Methodologies Radionuclides

Plutonium-239	Americium-241
Scintillation Counting	Alpha Spectroscopy
Alpha Spectroscopy	Gamma Spectroscopy
Neutron-induced autoradiography (NIAR)	
Fission track analysis (FTA)	

Detection Methodologies
Non-Radioactive Elements

Uranium
Cerium
Cobalt
Strontium
Lead
Iron
Others…

} Inductive Coupled Plasma Mass Spectroscopy (ICP-MS)

Other methods: Electron Paramagnetic Resonance (EPR)
Atomic Absorption Spectroscopy (AAS)

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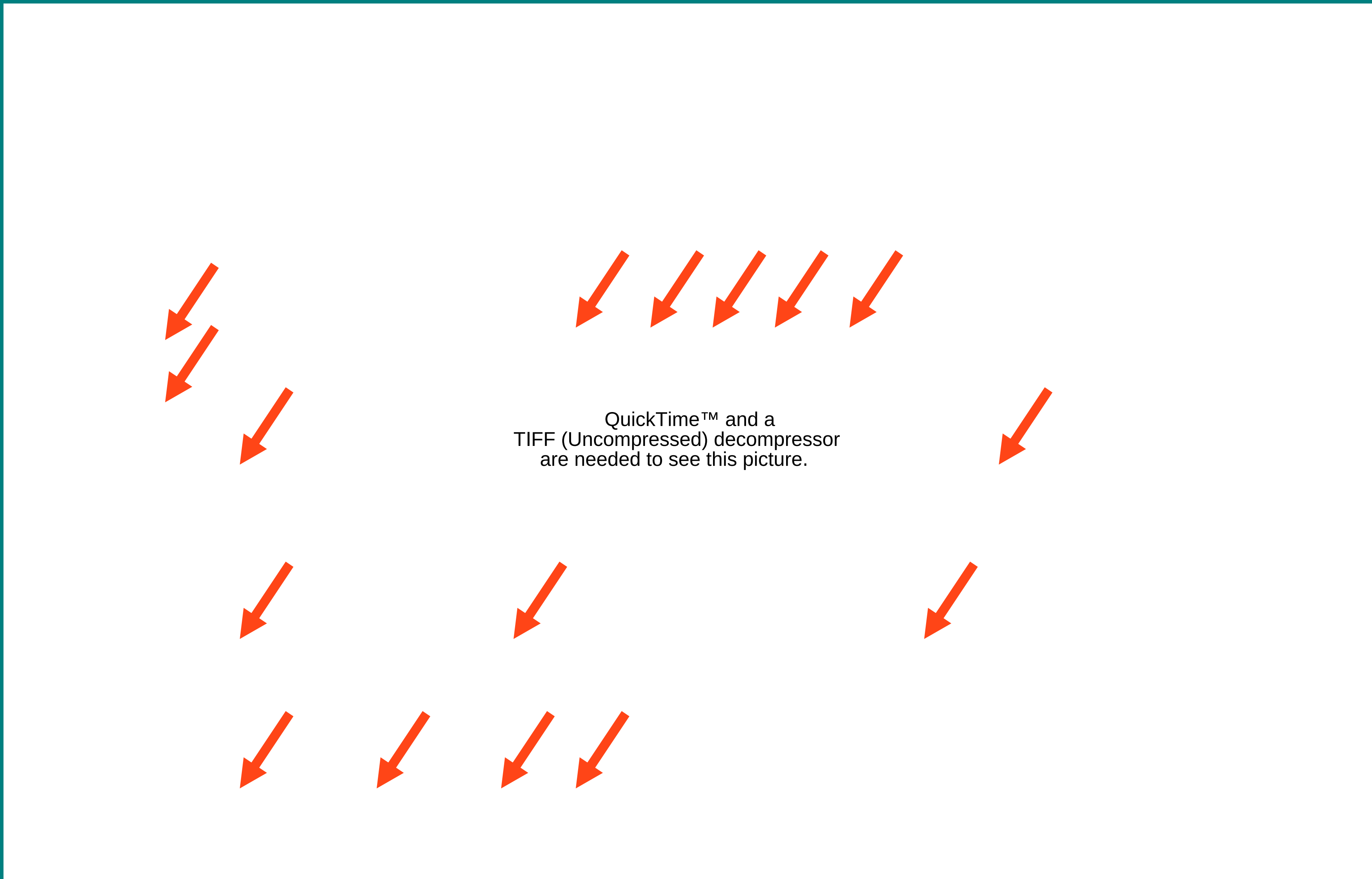
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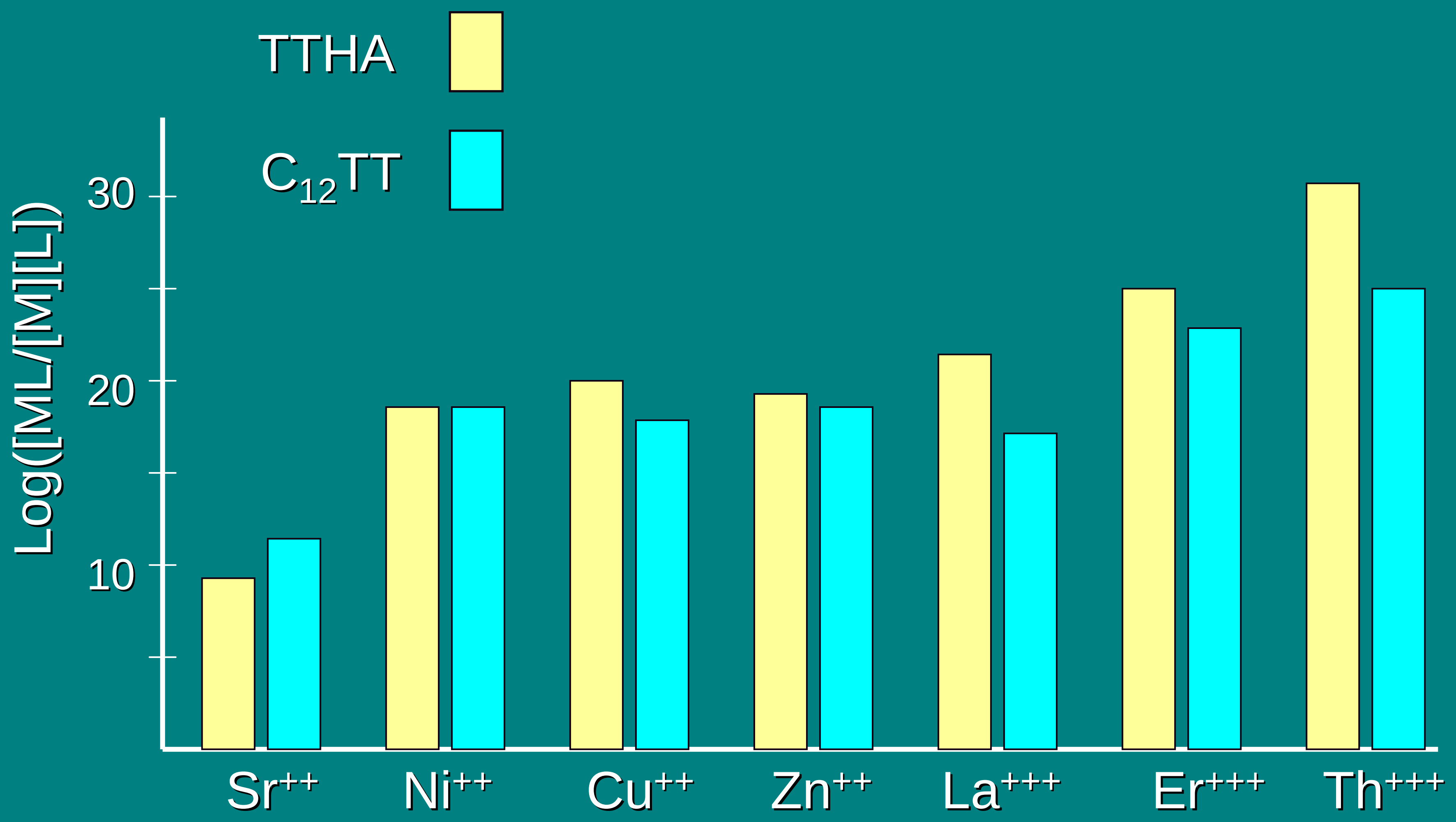
Log Stability Constants



Sonoda

Typical Animal Protocol

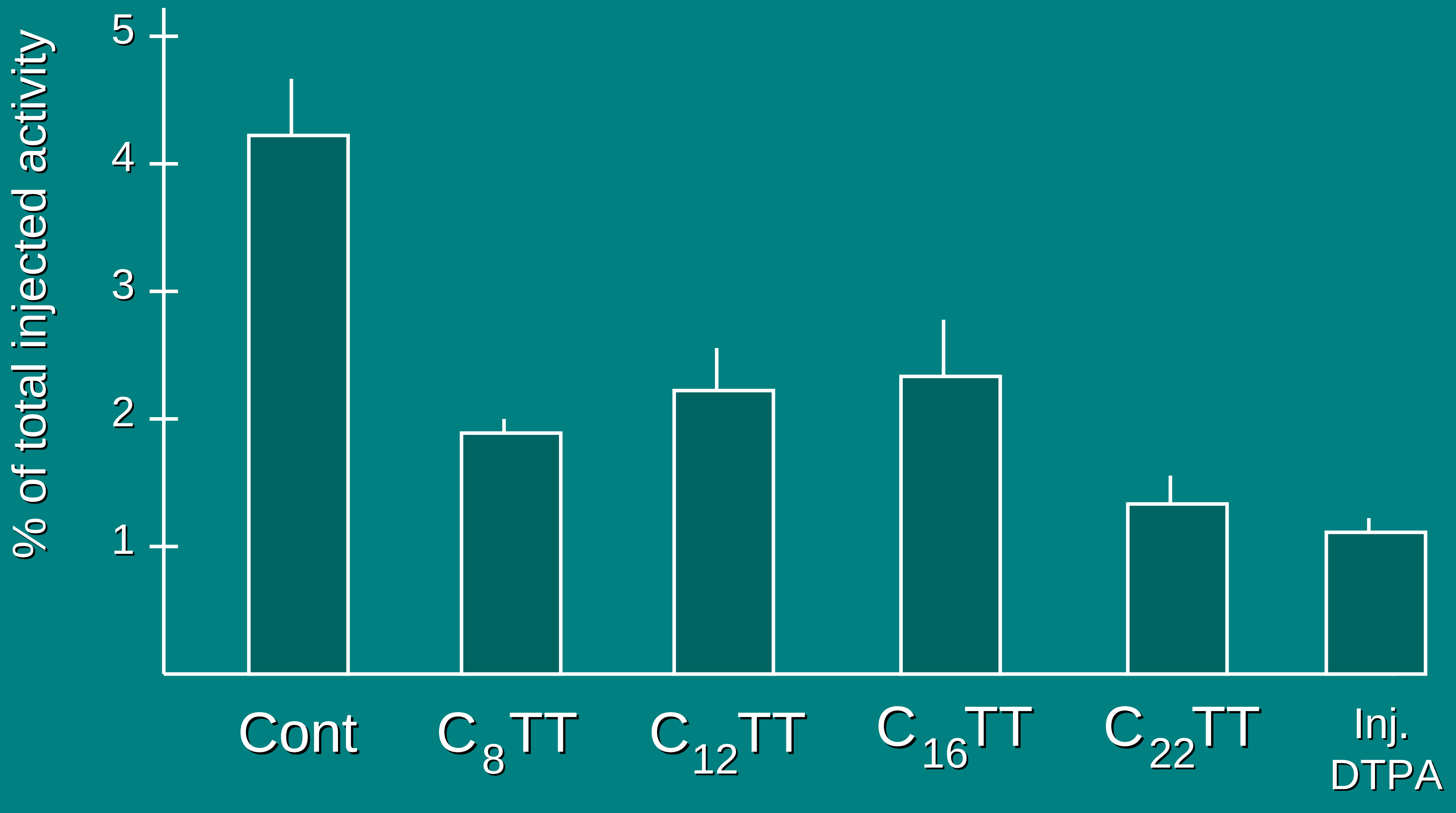
Actinides

- Expose rat/mouse to metal or nuclide (systemic)
- Wait: 0-14 days
- Begin oral treatment with C_xTT
  Intubation or add to food
- In-life measures: wt, food, water, feces, urine
- Organs: Bone, liver, kidney, spleen, other soft tissues

C_xTT Chelation of Pu^{239}

14 d Pu-239 - 30 d C_xTT with diet

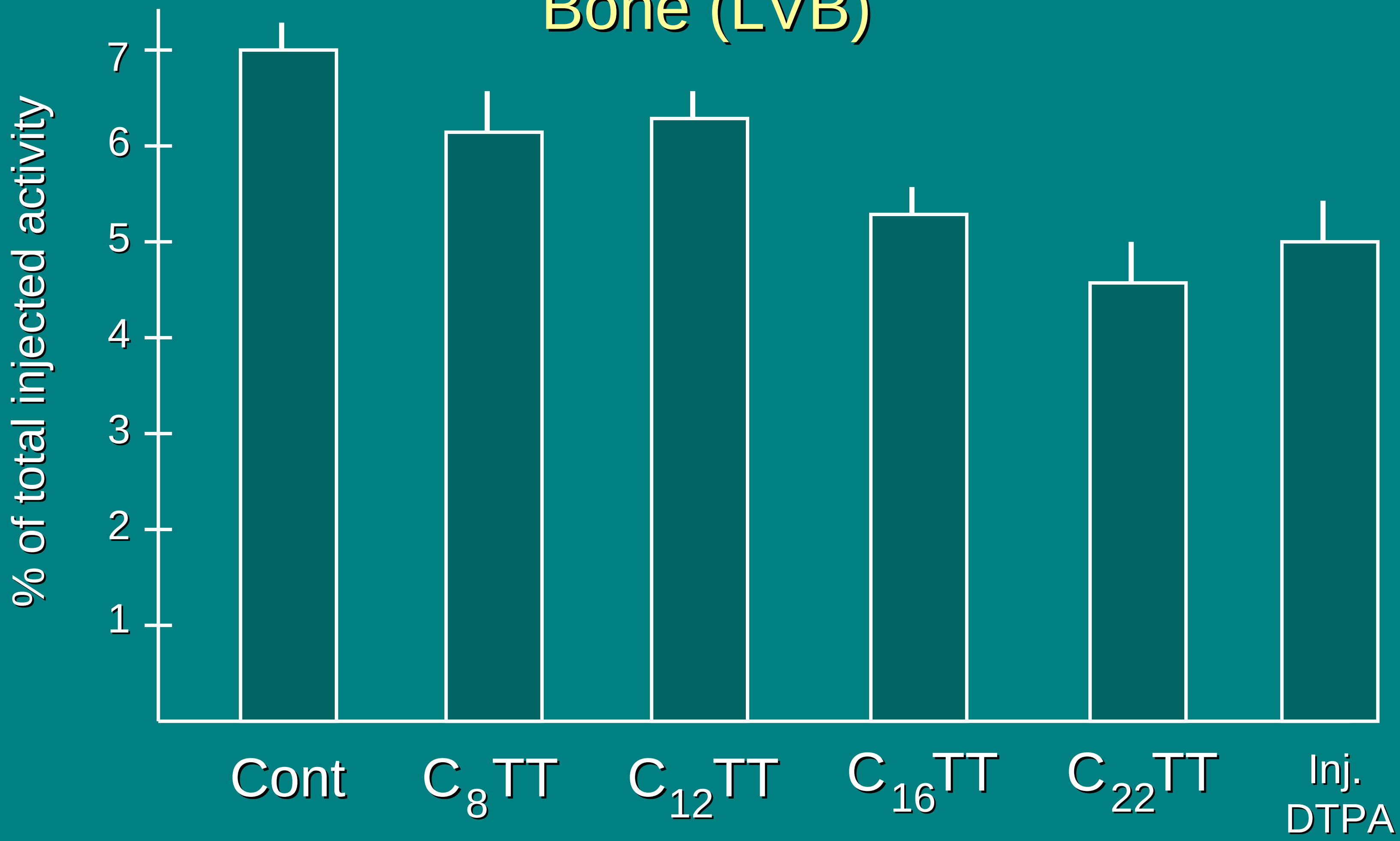
Liver



C_xTT Decorporation of Pu^{239}

14 d Pu^{239}; 30 d C_xTT with diet

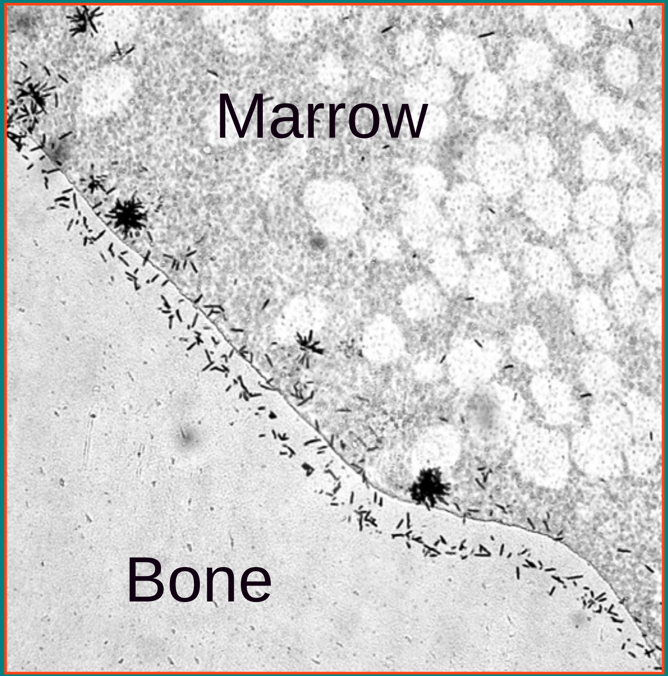
Bone (LVB)



Plutonium Deposition in Bone

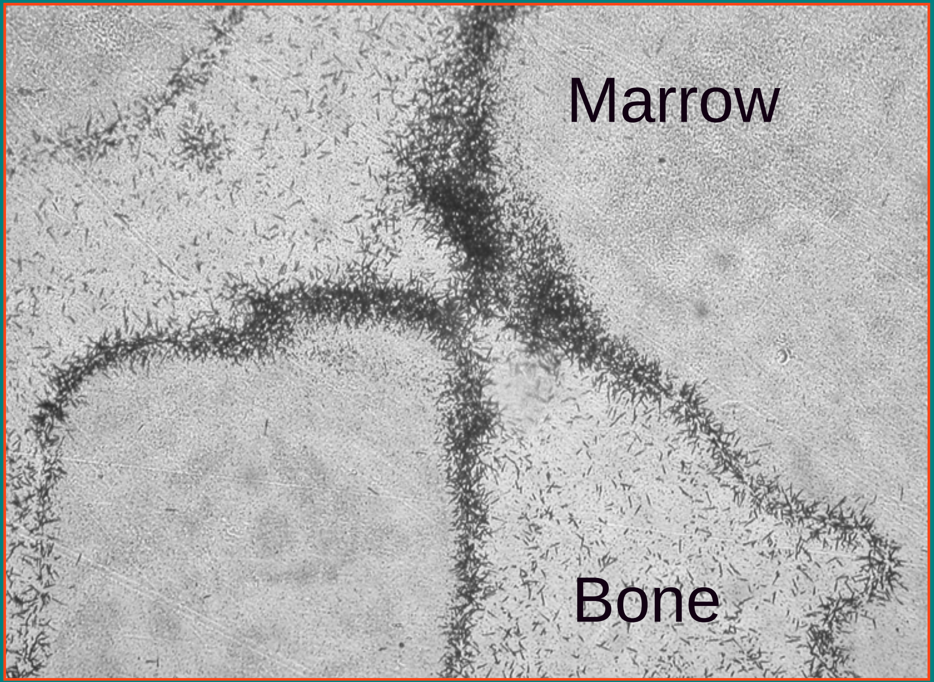
Neutron-Induced AutoRadiography (NIAR)

Dog



2 Mo after injection

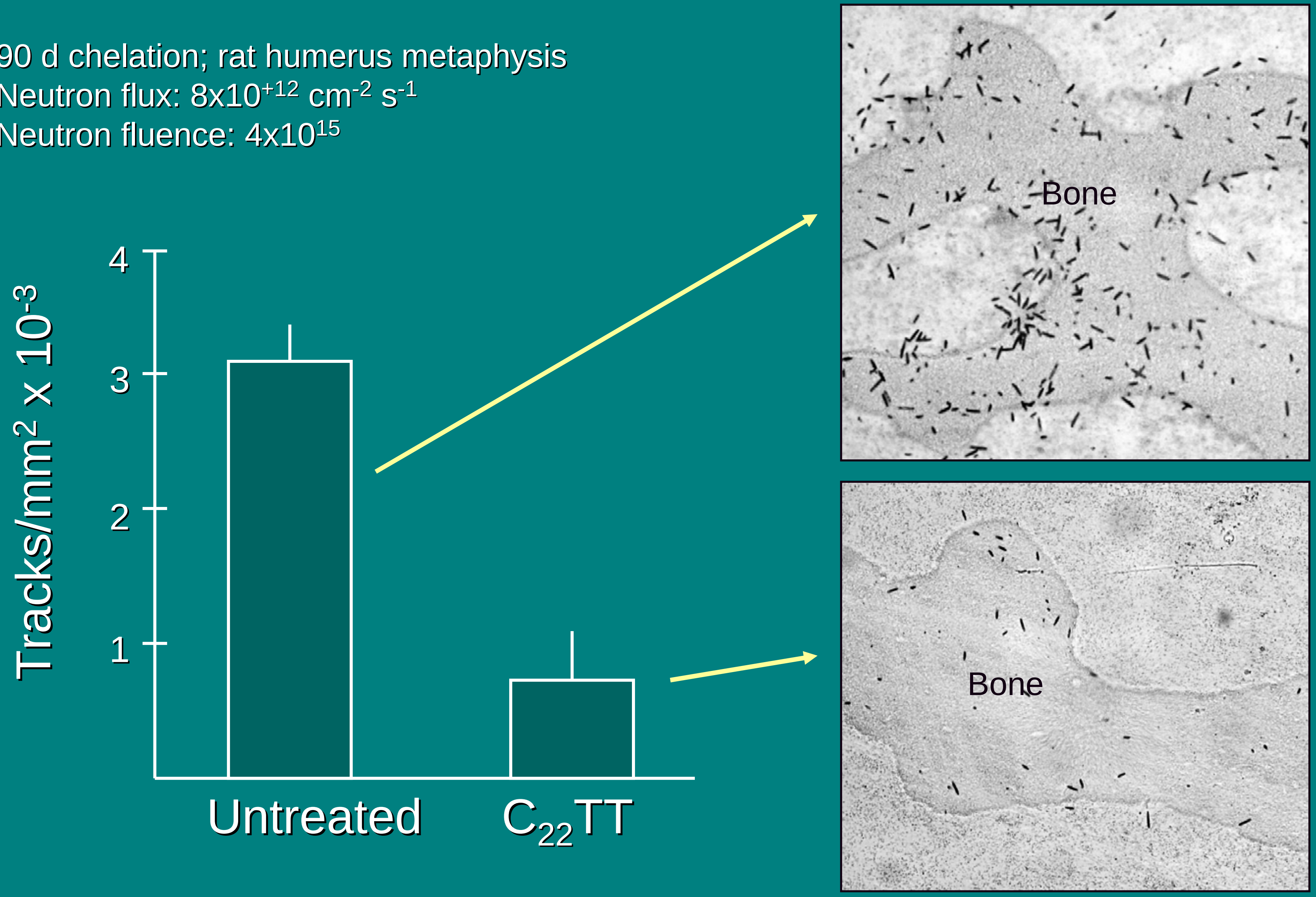
Human



About 40 years of industrial exposure;
With late in life liver disease

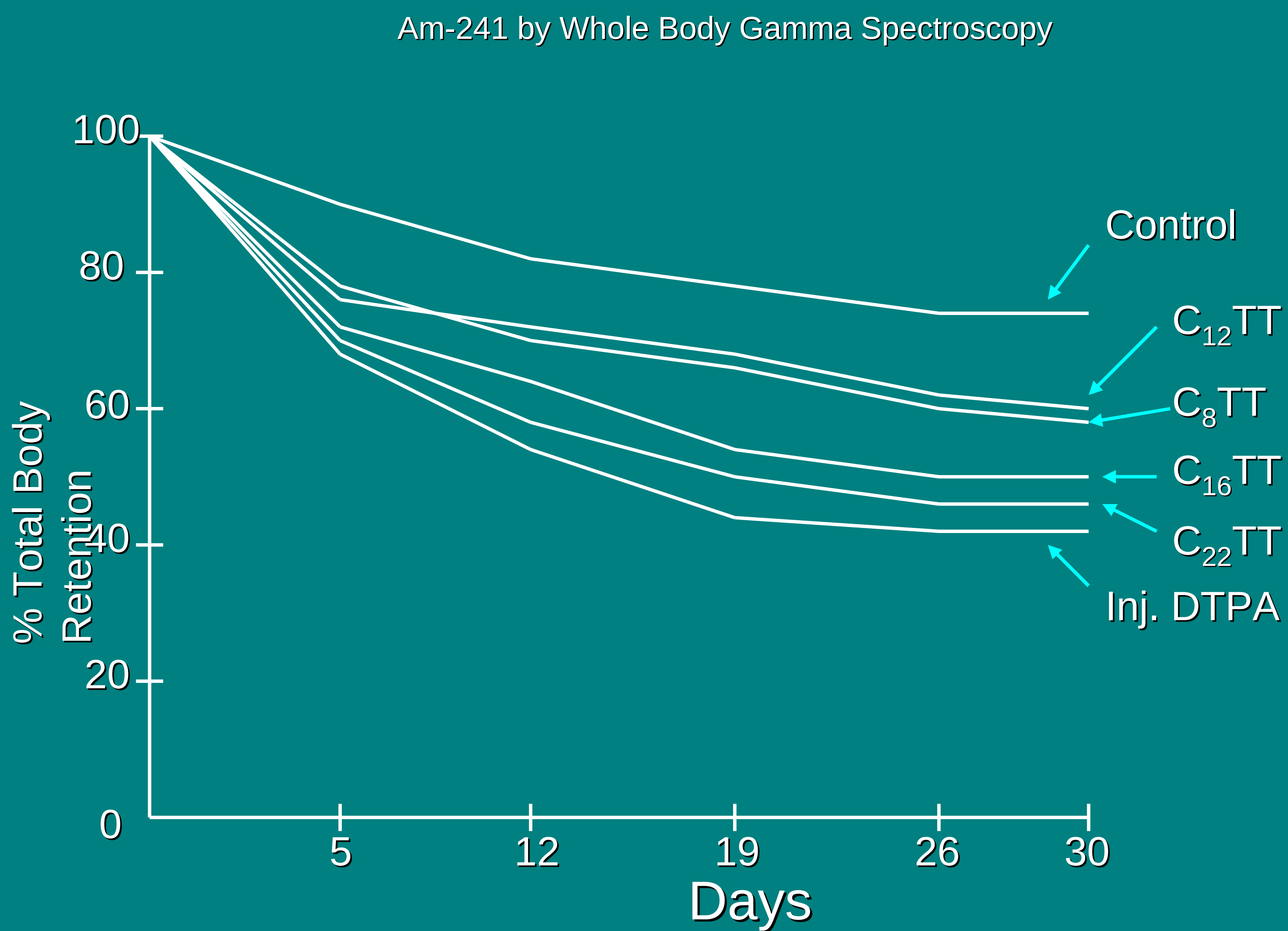
C_{22}TT on Redeposition of Pu^{239} in Bone

90 d chelation; rat humerus metaphysis
Neutron flux: $8 \times 10^{+12}$ cm^{-2} s^{-1}
Neutron fluence: 4×10^{15}



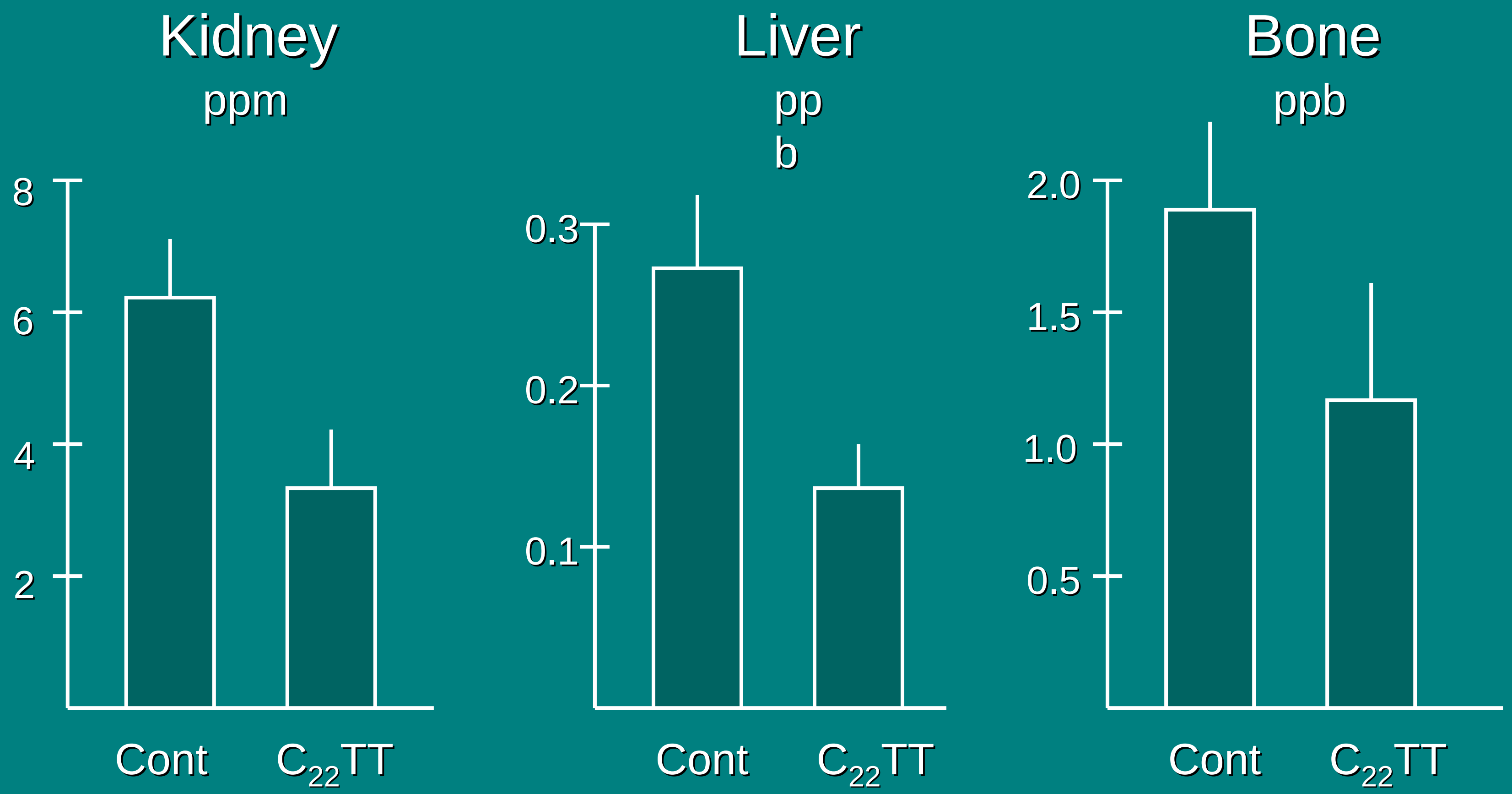
CxTT Chelation Am^{241}

14 d Am-241 - 30 d CxTT with diet



Uranium - $C_{22}TT$

10 d study: $C_{22}TT$ added to diet



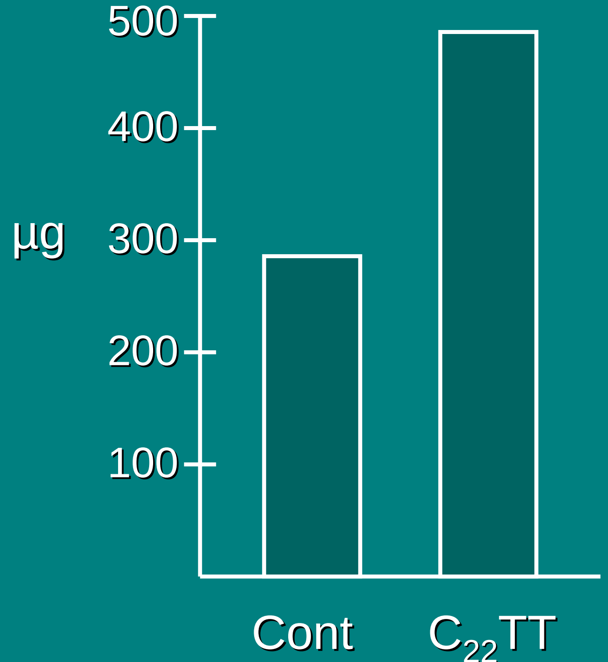
Preliminary data based on 3 rats per grou

Cobalt

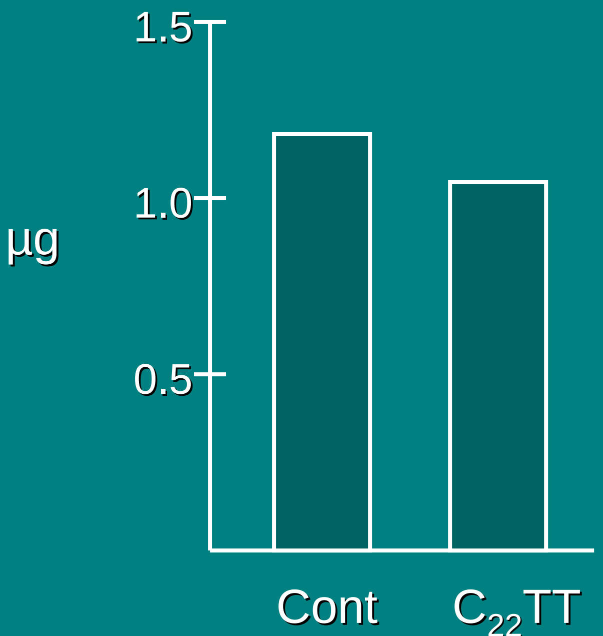
10 d, C_{22}TT by gavage, Co by ICP-MS

Total 24 hr excretion

After 1st C_{22}TT



Kidney Content



Preliminary data based on 3 rats per grou

Safety Issues with C_xTT

- Most experience is with $C_{22}TT$
- No formal toxicity testing
- Observations to date:
  - Well tolerated, especially when added to diet
  - Food, water consumption normal
  - Zn and Ca salts not yet tested
  - May expect trace metal depletion

- Other effects:
  - Increased bone mass in aged rodent models
  - Better coat and appearance

In Progress

- Bioavailability and PK
- Binding affinities - chain length
- More in vivo efficacy (U, Co, Ce, Sr)
- Bone/soft tissue Pu^{239} distribution with chelation

Summary

Amphipathic polyaminocarboxylic acid chelators

- Orally active
- Binding affinities are suitable for a number of
- metals/nuclides
- Amphipathic properties may be altered

  In vivo efficacy (oral administration) demonstrated for
- Pu, Am, U, Co, Pb, Fe (Studies in progress on Ce,
- Sr)
- Zn, Ca salts not yet tested in animals
- Relatively easy synthesis
- Stable

  Well tolerated

  Some beneficial properties in aged animal models

Research Team

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Melinda Krahenbuhl, Ph.D.: Nuclear engineering and
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Steven Kern, Ph.D.: Pharmacokinetics and preclinical
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William Johnson, Ph.D.: ICP-MS
Beth Bowman, M.S.: Animal services, lab management
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*Retired: July, 2007; now a consultant.
**Deceased, April 2007