# Mild and stable chelation strategies for small rare earth radiometals

BOROS Lab

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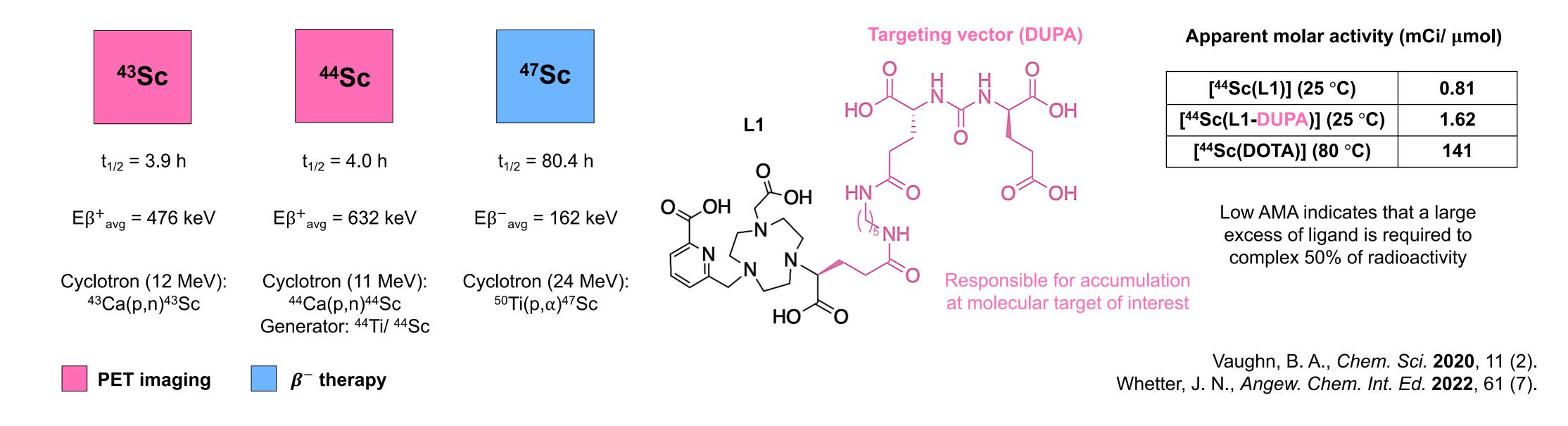
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# The challenge: Can we further improve chelator properties for Sc isotopes?

- Sc<sup>3+</sup> isotopes exhibit ideal properties for diagnostic imaging and therapy, well-matched to the pharmacokinetics of small biologics
- Yet, development of clinically applicable radiopharmaceuticals is impeded by poorly understood aqueous Sc<sup>3+</sup> coordination chemistry
- The gold standard chelator, DOTA, and our first-generation platform, L1, exhibit low apparent molar activity at room temperature

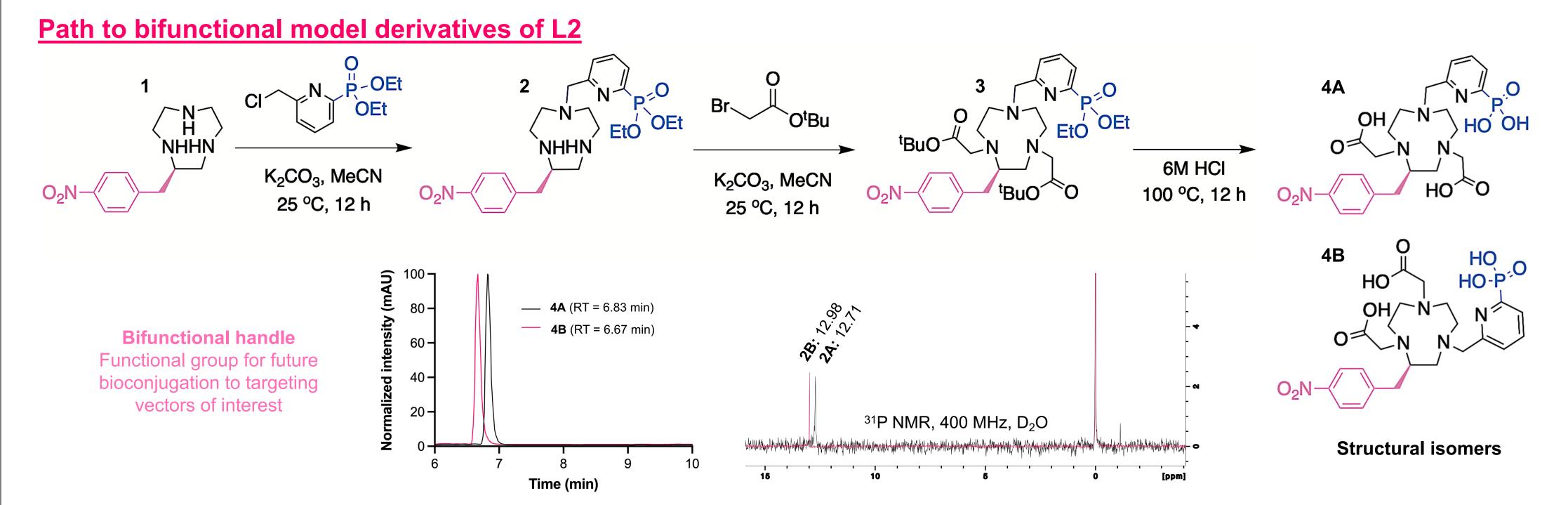


To harness Sc isotopes for radiolabeling of thermally-sensitive biologics, we seek high apparent molar activity at 25 °C.

# Computational structural determination (DFT) Phosphonate functionality Highly polarized, electron rich donor Macrocyclic chelator High kinetic inertness to avoid decomplexation in vitro and in vivo Tinner-sphere H<sub>2</sub>O Verified with solution and gas-phase studies Further limited solvent access due to capping by phosphonate

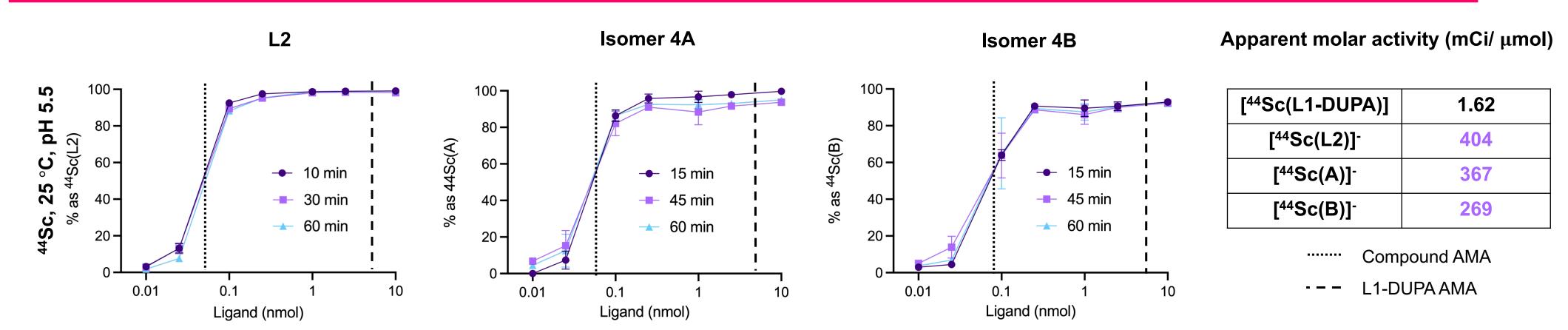
We hypothesize that introduction of phosphonate functionality will impart rapid chelation kinetics with scandium.

# Solution thermodynamics: What species are present under relevant pH conditions? **Observed L2 species Technique: UV Speciation** $[Sc(L2)(OH)]^{2-}$ [Sc(H**L2**)] [Sc(**L2**)] 2. Adjust pH 3. Measure UV n = 0, 10.1 mM **Ligand** 0.1 mM **Sc**<sup>3+</sup> 0.01 M HCI 0.1 M KCI pH 7.4 pKa<sub>3</sub> pH 7.4 [Sc(**L2**)]-Sc<sup>3+</sup> [Sc(**L1**)] ၂ 80 **Key features** Complexes form below pH 2 (pKa<sub>1</sub>) 1:1 metal ligand complexes dominate at physiological pH **Hydroxy-coordinated species form** above pH 8 [Sc(**L1**)(**OH**)]- $[Sc(L2)(OH)]^{2-}$ [Sc(H**L2**)] рН Introduction of phosphonate functionality in L2 shifts complex formation pKa to a lower pH.



Functionalization of L2 affords two structural isomers that can be chromatographically separated.

## Radiochemical synthesis: Does our second-generation chelator platform exhibit improved properties with 44Sc?



Yes, L2 and its derivatives exhibit drastically higher apparent molar activity at room temperature than L1-DUPA.

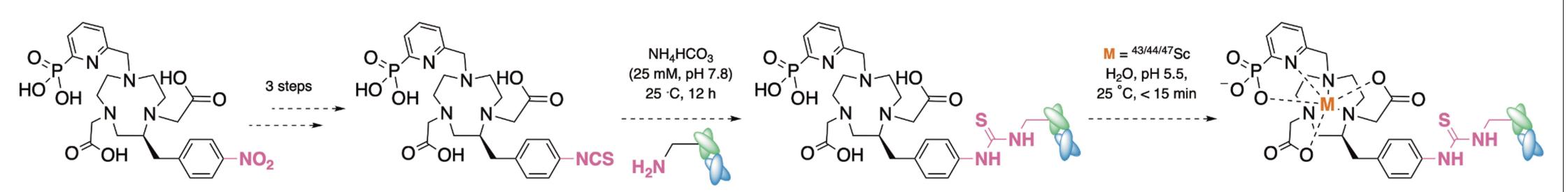
### **Conclusions:**

Our second-generation phosphonate-based chelator platform, L2:

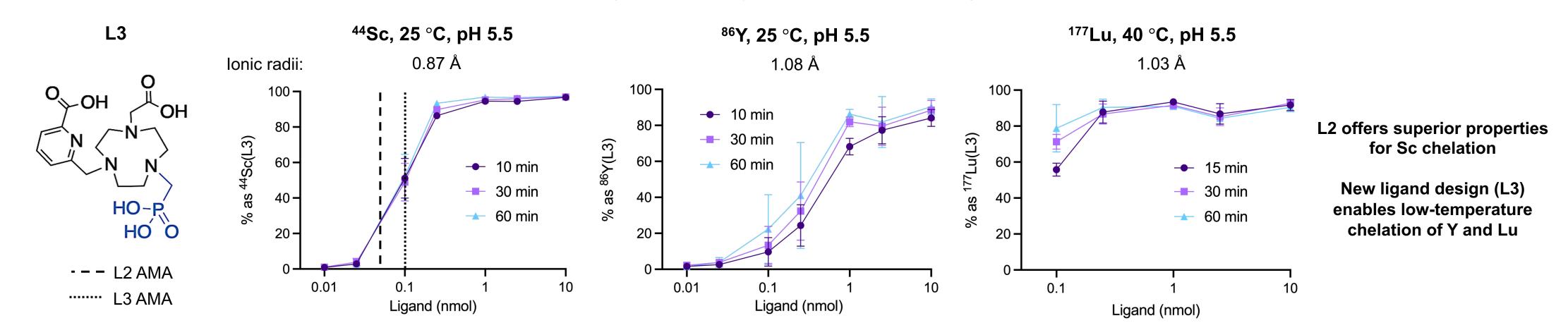
- Successfully stabilizes Sc<sup>3+</sup> under conditions relevant for radiochemical synthesis and biological applications
- Affords <sup>44</sup>Sc complexes with improved apparent molar activity (AMA) under conditions compatible with thermally-sensitive biologics

### **Future outlook:**

1. Path to bioconjugation of thermally-sensitive biologics



2. Toward chelation of small, rare earth radiometals (scandium, yttrium, and lutetium) for theranostic applications



### **Acknowledgements:**

This work was supported in part by Department of Energy Isotope Program's grant DE-SC0022550, the Horizon-Broadening Isotope Production Pipeline Opportunities (HIPPO) Program.



EB acknowledges the Gordon & Betty Moore foundation for generous support of this work through the 2020 Moore Fellowship. JNW gratefully acknowledges Aeli P. Olsen and Wilson Lin for experimental support.