The Dosimetry Paradox of AGuIX Radiosensitizer Nanoparticles: Shifting from Macroscopic Dose Enhancement to Microdosimetric Specific Energy Distributions

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ABSTRACT

Purpose: Preclinical studies combining radiation with gadolinium-based AGuIX nanoparticles show potent radiosensitization effect. However, physics simulations to date show a lack of macroscopic dose enhancement. We address this by shifting from absorbed dose (D) to microdosimetric specific energy (z). We test the hypothesis that the therapeutic benefit is linked to alterations in the stochastic distribution of energy deposition events at the nanoscale, driven by short-range electron cascades arising from AGuIX nanoparticles.

Methods: We performed Monte Carlo simulations using the TOPAS toolkit (Geant4 code). A cell model incorporating 177Lu decays from the membrane generated a phase space source entering lysosomes. These particles were transported through a lysosomal geometry containing explicit AGuIX Gd-nanoparticles (1.5 nm radius) or water-equivalent controls. We used G4Em-Livermore for nanoparticle (AGuIX/control) interactions and G4Em-DNA for low-energy track structure in water. We scored both radial dose profiles and specific energy (z) distributions in nanometric voxels proximal to the nanoparticles to quantify stochastic energy deposition patterns.

Results: Radial dose profiles (D) showed negligible differences in Dose Enhancement Factor (DEF). However, microdosimetric analysis showed a shifted specific energy (z) probability density function in voxels proximal to the nanoparticles. While the mean specific energy remained comparable, the AGuIX group showed an increase in the frequency of high-z events (energy deposition spikes). This tail corresponds to the localized, high-density energy transfer characteristic of Auger cascades, which is conventionally averaged out in standard dosimetry.

Conclusion: The radiosensitizing efficacy of AGuIX is driven by stochastic, high-specific-energy events, rather than cumulative dose enhancement. Standard macroscopic dosimetry obscures these nanometric spikes. Consequently, specific energy (z) provides the mechanistic link between physics and biology, establishing it as the superior metric for predicting efficacy in high-Z nanoparticles radiosensitization.

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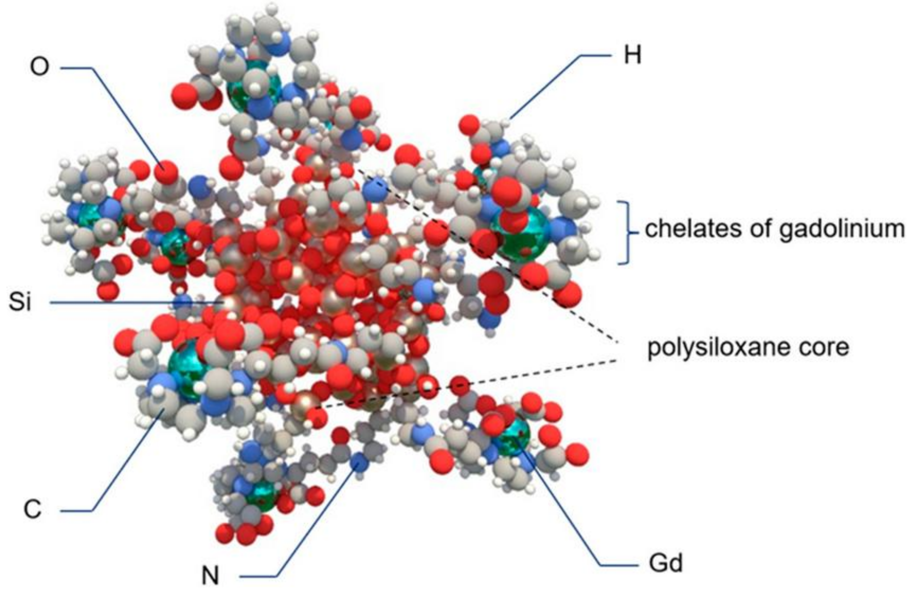
INTRODUCTION

Gd-based **AGuIX nanoparticles** are currently in phase II clinical trials as **theranostic agents** in radiotherapy. They selectively target the tumor via enhanced permeability and retention effect, and there they provide **contrast** for **MRI** and act as **radiosensitizers** upon irradiation.



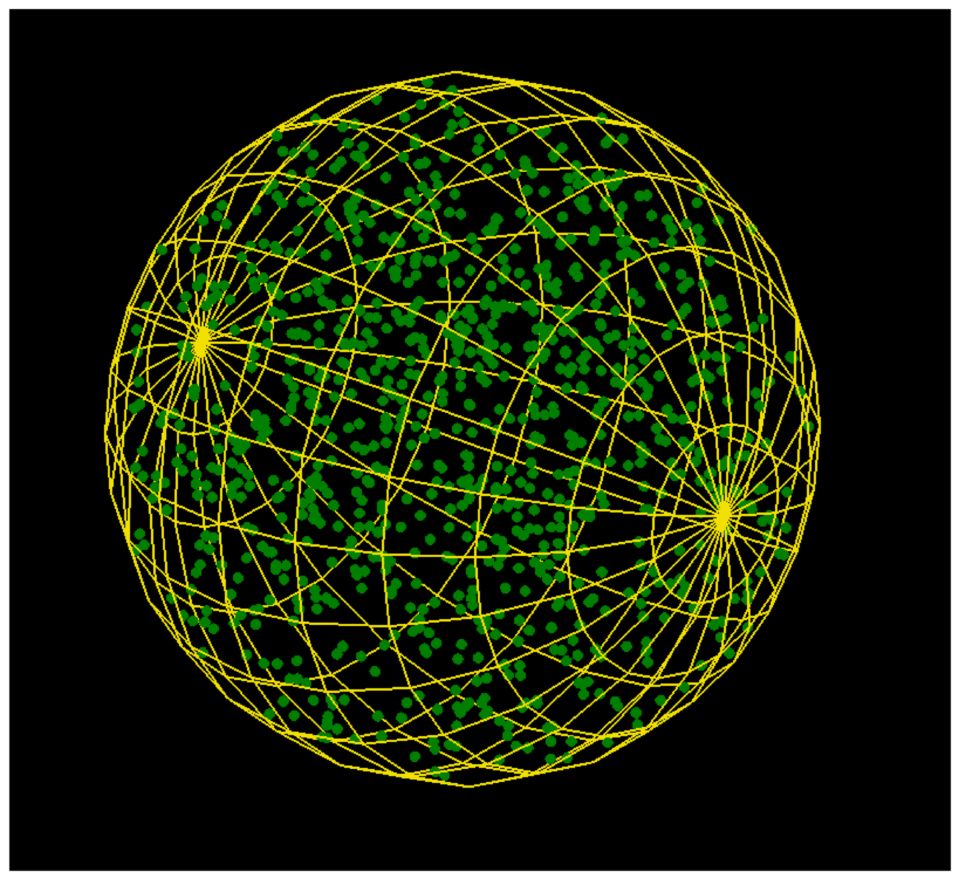
Classically, the mechanism of action of metal nanoparticles has been associated to an overall dose enhancement factor (DEF) triggering a downstream radiosensitization effect. However, calculations performed to date with AGuIX show **no macroscopic dose enhancement** effect.

Here, we study the distribution of dose around AGuIX nanoparticles and show that while overall DEF is unchanged, the **spatial distribution** of dose shows **localized high-density energy transfers** characteristic of **Auger cascades**.

METHODOLOGY

We performed staged **Monte Carlo** simulations using the **TOPAS** toolkit (Geant4) as the main physics engine, and TOPAS-nBio for chemistry. We define a two-stage simulation chain:

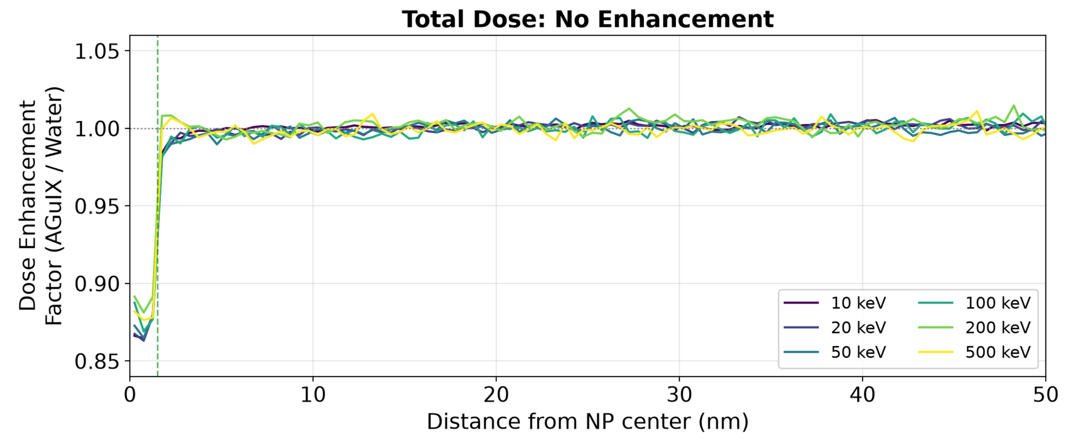
1. **Lysosome scale**: a 0.25 µm radius water sphere containing 370 000 AGuIX NPs (100 mg AGuIX/mL, extrapolated from electron microscopy measurements).
2. **Nanoparticle scale**: a single AGuIX nanoparticle (1.5 nm radius) centered in a 200 nm water sphere world.



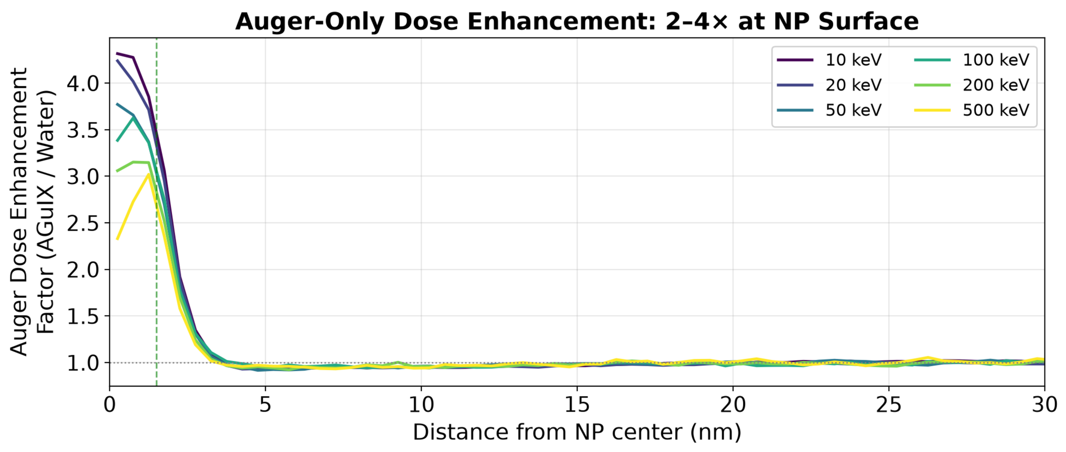
We used electrons and photon sources, scoring magnitudes like dose to medium, Auger-specific dose, track-specific characterization and dose, and spatial per-cascade radical yield.

GENERAL DEF VS AUGER DEF

Consistent with existing literature, AGuIX shows **no overall radial dose enhancement factor**, even at the nanometer scale.



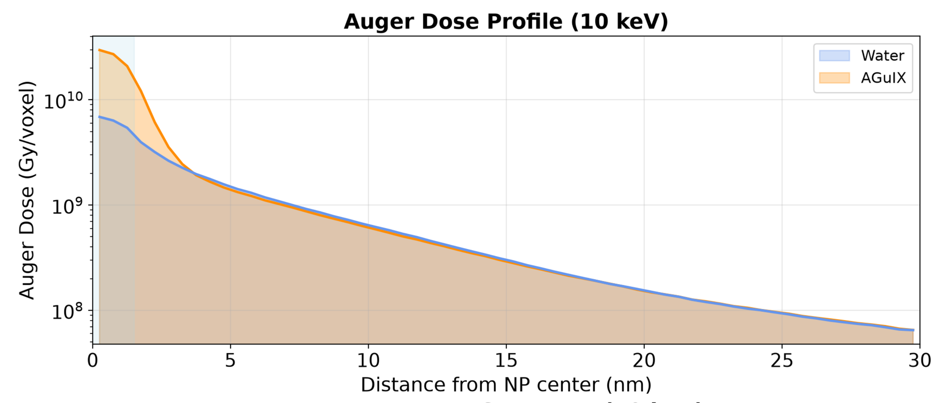
However, AGuIX produces a **higher yield of Auger electrons (3.5 - 3.9x** for electron energies 10-500 keV), significantly increasing the Auger-only dose in AGuIX over water at the nanoparticle surroundings. However, it is worth noting that Auger processes contribute minimally to the overall dose.

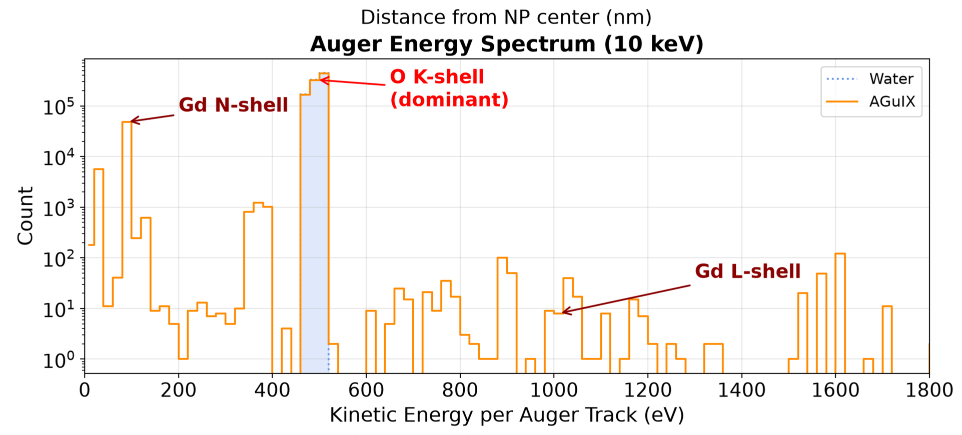


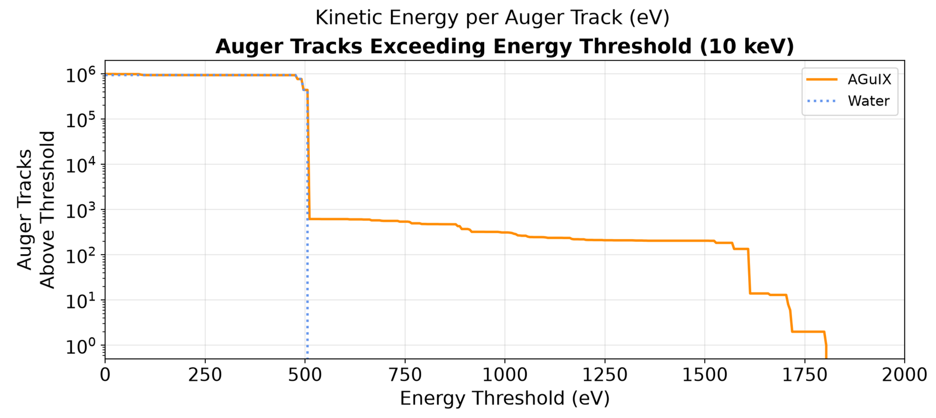
E (keV)	Augers/NP (AGuIX)	Augers/NP (Water)	Ratio	N>1keV (AGuIX)
10	130,234	33,288	3.91	736
20	74,348	19,911	3.73	582
50	35,941	9,992	3.60	320
100	21,408	6,055	3.54	186
200	13,226	3,806	3.48	127
500	9,576	2,749	3.48	106

AUGER CHARACTERIZATION

The excess Auger production comes primarily from **Gd N-shell Auger and** to a lesser extent **L-shell** for electron irradiations (see figures below). The effect is two-fold: a population of **Augers that deposit the dose locally on the AGuIX vicinity**, and a smaller population of **higher energy electrons that water cannot produce**.



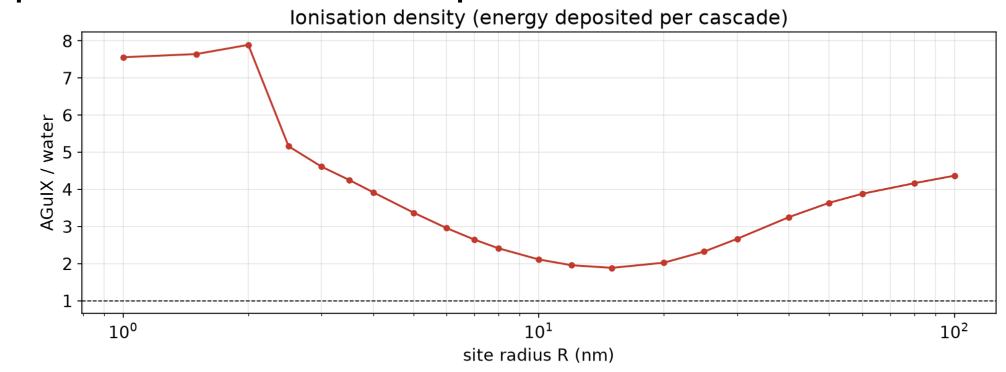


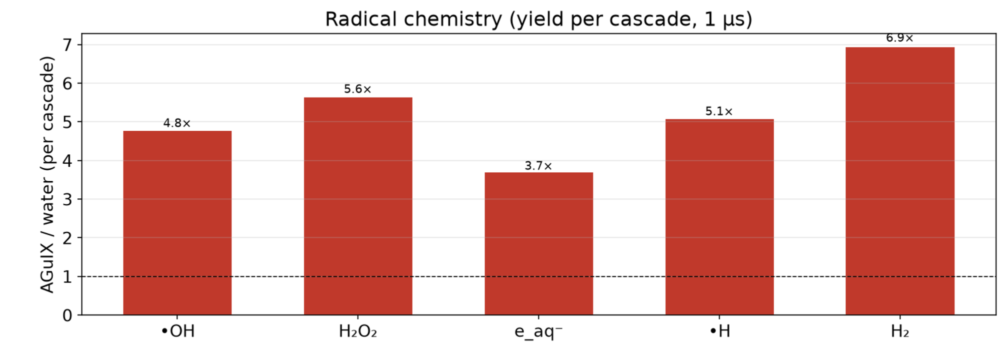


For photon irradiations, the K-shell produces higher energy tracks, and larger local Auger cascades.

THE BIOCHEMICAL BRIDGE

Extending the Auger analysis to track-structure and radiation-chemistry simulations show the Gd effect on different metrics: energy deposition, ionization clustering, and radical yield, all showing consistent AGuIX excess in the peri-NP water. This could **bridge the physics** (Auger cascades) to the **biological effect** through **reactive oxygen species** exactly where they could drive lysosomal membrane damage. Below, the figures picture these effects for a photon 55 keV beam, pure-water track structure.





CONCLUSIONS

- **AGuIX produces no macroscopic dose enhancement**, consistent with prior reports and now confirmed down to nanometer scale.
- Instead, **AGuIX generates 3.5-3.9x more Auger electrons,** creating a **localized, high-density energy deposition** (Auger DEF 2-4x) confined to a few nm of the NP surface.
- **This excess is a Gd-specific,** spatially-bound, high-LET source that **water cannot produce**. This affects ionization clustering and radical chemistry, plausibly **bridging** the **physics** of Auger cascades to **ROS-induced lysosomal membrane damage.**
- **Take-home:** AGuIX **radiosensitization** is driven by the **spatial concentration** and character of **nanoscale energy deposition**, not by average dose, so predicting efficacy requires **nanodosimetric and radiochemical metrics, not overall dose enhancement**.

LET'S CONNECT!

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