TRANSFORMATIONS OF L-DOPA DURING THE SYNTHESIS OF GOLD-BASED NANODELIVERY SYSTEMS FOR LAT-1 TARGETING

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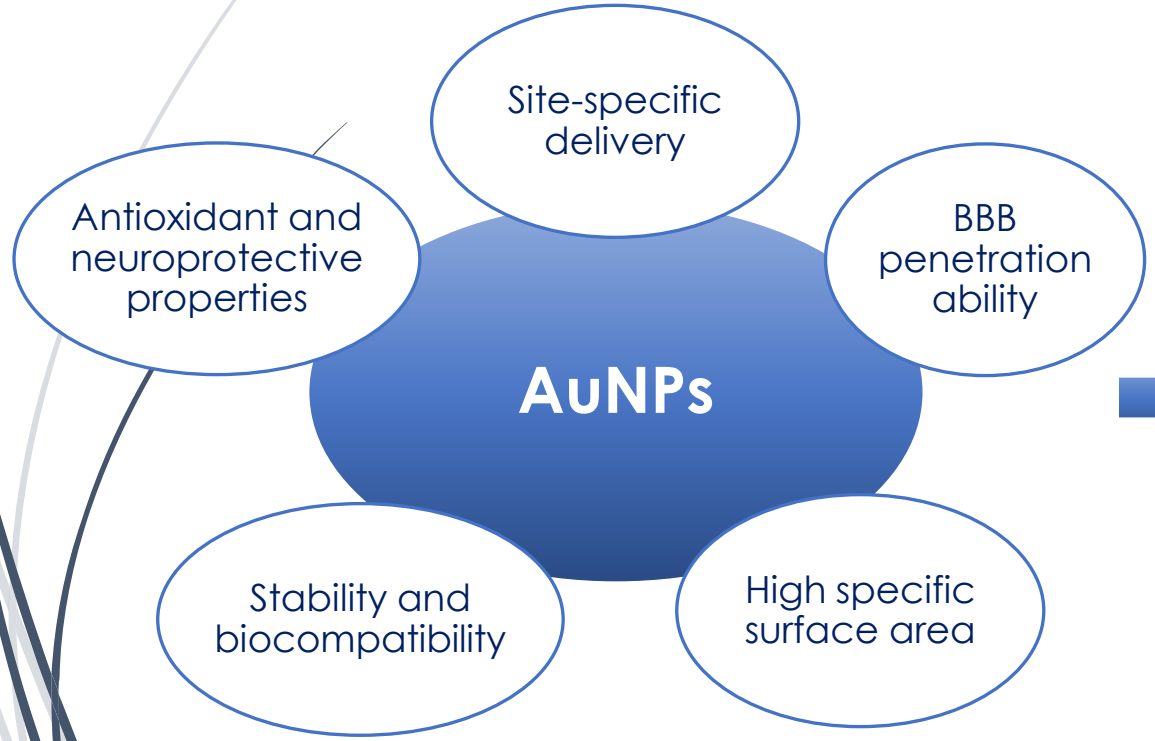
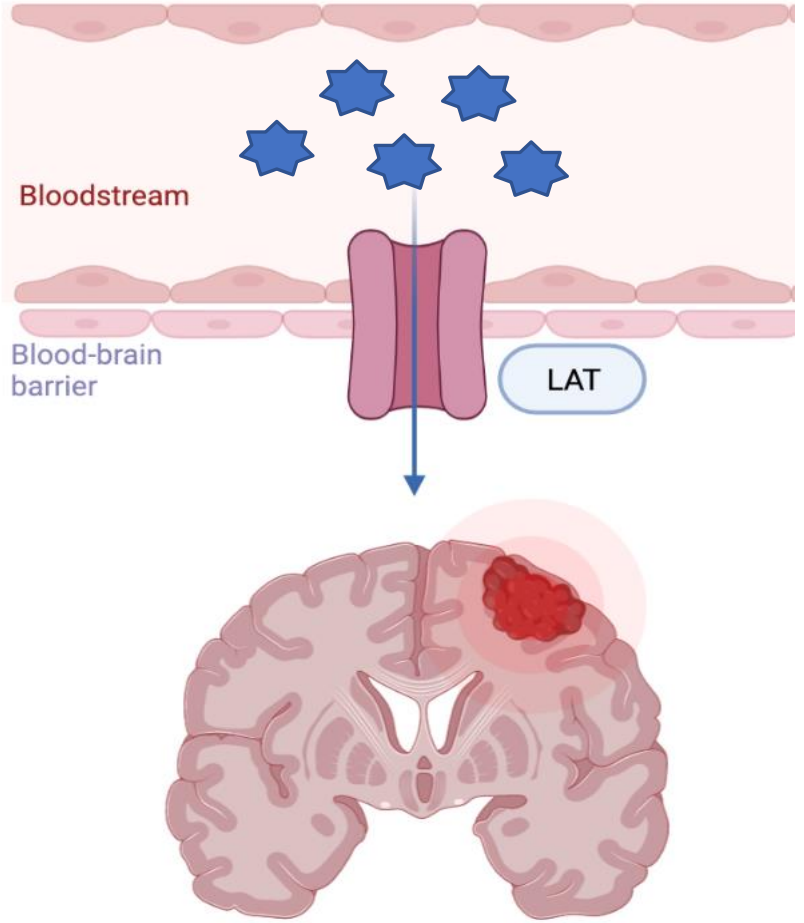
INTRODUCTION

- LAT-1, the large neutral amino acid transporter-1, plays a crucial role in cancer growth and proliferation, making it a promising biomarker for imaging and treating human malignancies
- overexpressed in various cancer cells, including glioma → promising target in the treatment of brain tumors
- LAT-targeted drug delivery systems with blood-brain penetration ability

NEW THERAPEUTIC APPROACHES:

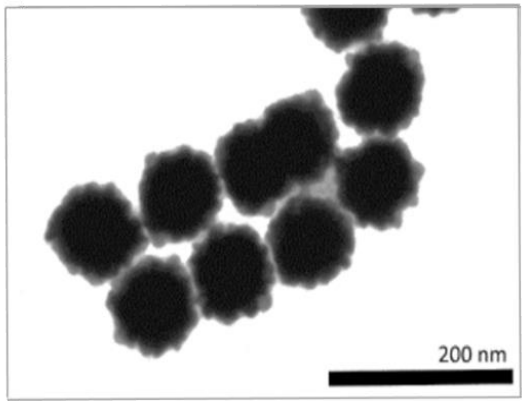
- nanotechnology- drug-delivery nanosystems→ gold nanoparticles (AuNPs) functionalized with L-DOPA



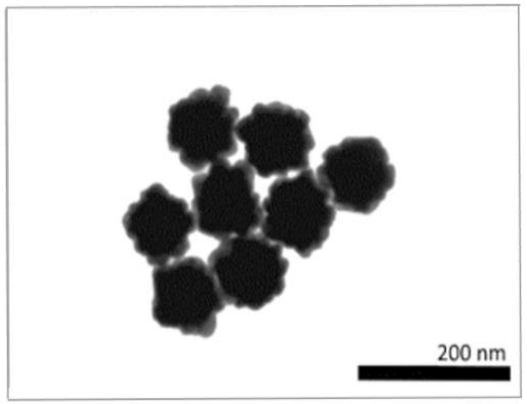


- 2 different synthetic protocols were investigated by changing the molar ratios of reactants, Au salt and L-DOPA

[Au]:[L-DOPA] = 1:6



[Au]:[L-DOPA] =2:1



pH = 3.15 - 3.25

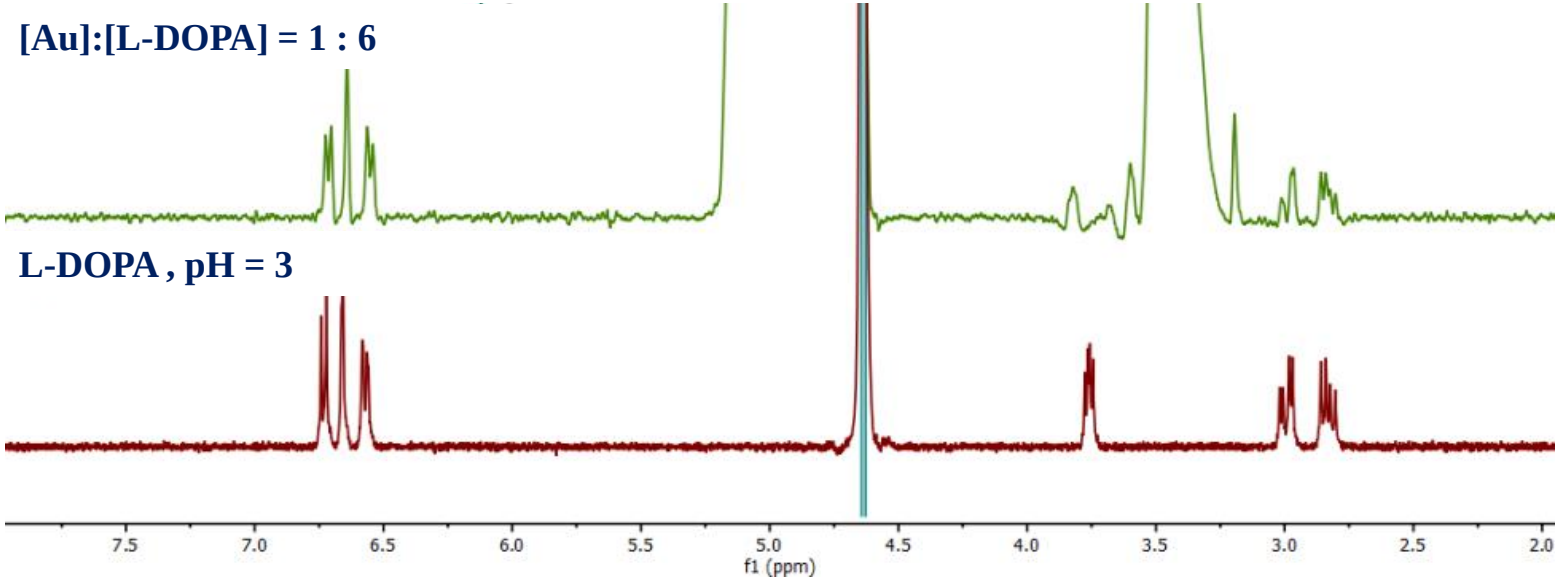
[Au]:[L-DOPA]	*d* (nm)	d_H (nm)	ζ (mV)
1:6	88.3 ± 4.5	116.8 ± 0.6	-31.3 ± 0.9
2:1	94.0 ± 5.1	119.9 ± 0.4	-41.1 ± 1.3

WHAT'S GOING ON AT THE NANO-BIO INTERFACE?

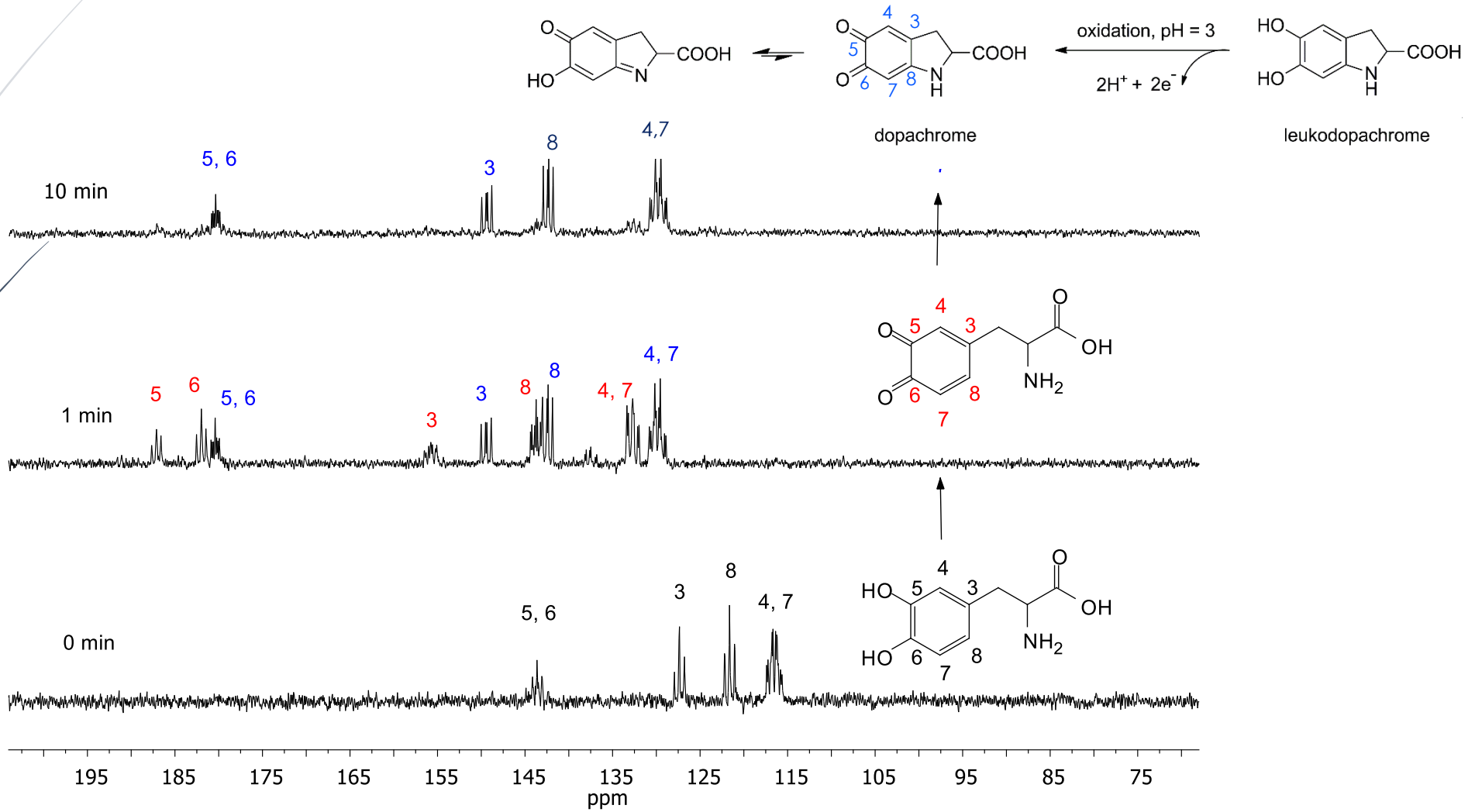
- in the acidic pH, gold salts can promote L-DOPA transformations such as oxidation, cyclization, and polymerization
- to avoid binding structurally altered molecules to the nanosurface and prevent any negative impact on human health, it is important to consider these transformation patterns
- behaviour of L-DOPA upon interaction with a gold nanosurface in acidic pH was investigated by using a combination of nuclear magnetic resonance (NMR) spectroscopy and computational methods

NMR results

- if the synthesis is performed with a **large excess of L-DOPA** ([Au]:[L-DOPA] = 1 : 6) → L-DOPA itself was bound to nanosurface during the preparation of AuNPs



- if the synthesis is performed with an **excess of Au salt** ([Au]:[L-DOPA] = 2 : 1) → the oxidation of L-DOPA occurred → oxidation products attached to the gold nanosurface

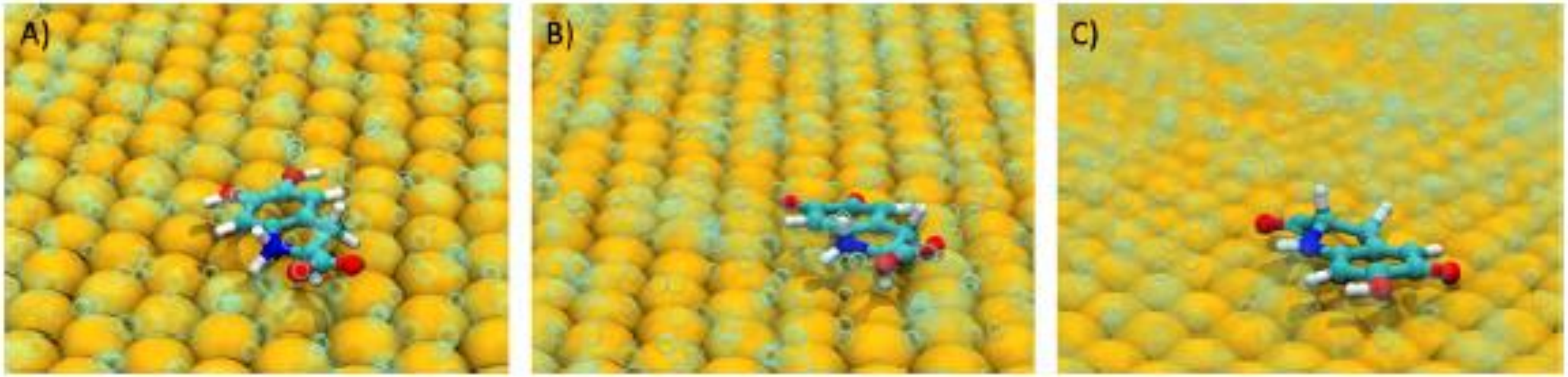


DFT calculations

- to assess the effect of gold nanoparticles on the cyclization rate, the reactant dopaquinone, transition state, and product (leukodopachrome) were modeled as structures complexed to the neutral cluster Au_n, where $n = 2$, 4, or 6
- the formation of cyclized products is strongly exergonic, i.e. the leukodopachrome are more stable than the starting dopaquinone
- In the case of metal-free and Au-assisted reactions, cyclized products were 25 - 75 kJ/mol stable → reaction is thermodynamically favored

Au_n	Stationary point	ΔG_{298} (kJ/mol)
n = 0	R	0.0
	TS	+63.3
	P	-85.0
n = 2	R	0.0
	TS	+94.1
	P	-38.9
n = 4	R	0.0
	TS	+101.9
	P	-17.7
n = 6	R	0.0
	TS	+91.6
	P	-63.8

MD simulations



LEUKODOPACHROME
ΔG_{bind} = −160.9 kJ/mol

DOPACHROME
ΔG_{bind} = −182.9 kJ/mol

DOPACHROME TAUTOMER
ΔG_{bind} = −125.0 kJ/mol

- all functional groups are involved in the interaction between the oxidized species and the Au surface
- all three molecular adsorption processes are exergonic (i.e., thermodynamically spontaneous)
- dopachrome has the highest affinity for the Au nanosurface → surface of prepared AuNPs is modified only with dopachrome

CONCLUSION

- the obtained results represent valuable mechanistic data about the binding events at the surface of AuNPs to encourage their application as a drug-delivery systems in the brain cancer therapy

THANK YOU FOR YOUR ATTENTION!

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