Interfaces between atomically precise metal nanoparticles and biomolecules: Prospects and challenges

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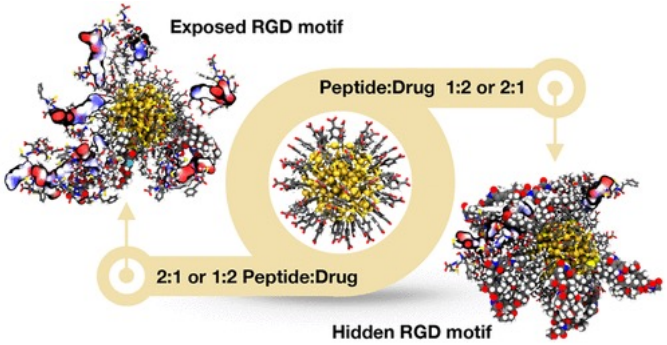
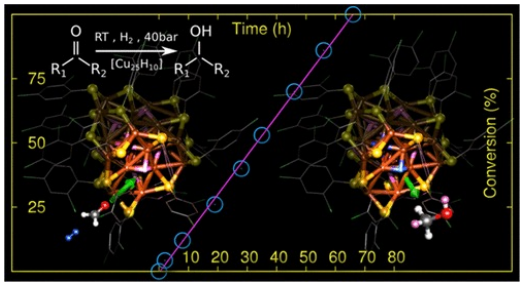
From climate change to cancer

Computational Nanoscience group, NSC, University of Jyväskylä

Nanoparticles are everywhere but we do not see them nor do we understand them well. That is why fundamental research into their physical, chemical and biological properties are needed. Our group uses and develops multiple computational and machine learning methods to investigate metal-based and organic nanoparticles whose **atomic structure is known or can be modelled to atomic precision**.
Currently we want to understand:

- How clustering of organic molecules initiates formation of aerosol particles?
- How metal nanoparticles work as thermocatalysts and electrocatalysts?
- How gold-based nanoparticles work as sensors in a biological environment?
- How gold-based nanoparticles work as targeted carriers for cancer drugs?





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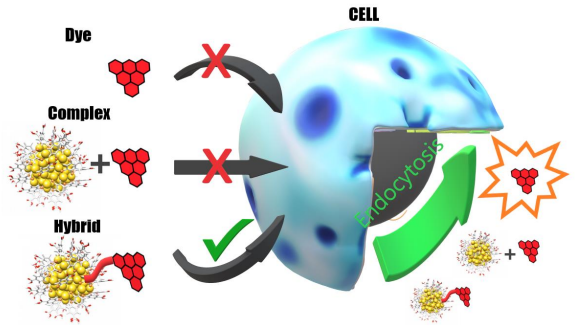
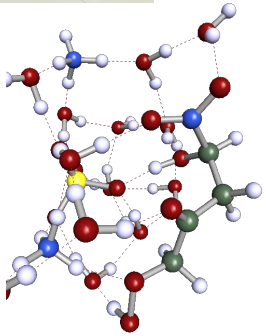
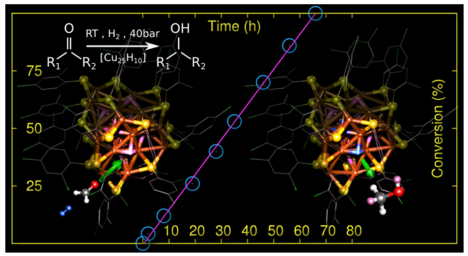
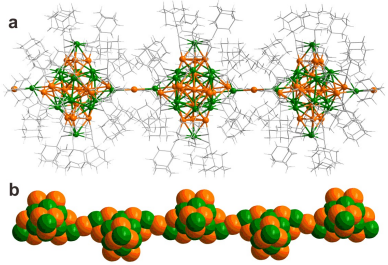




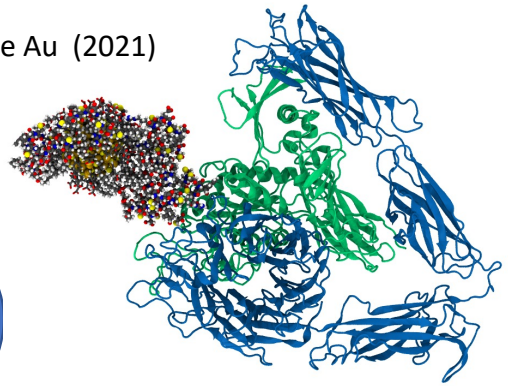


ACS Nano
13, 5975 (2019)

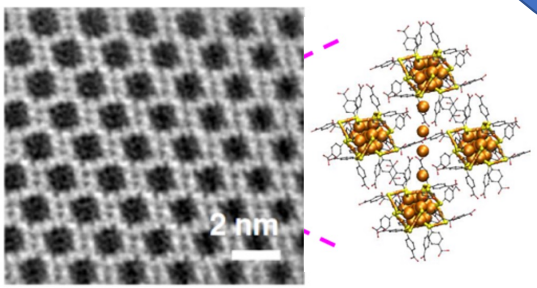
Nature Comm **11**, 2229 (2020)

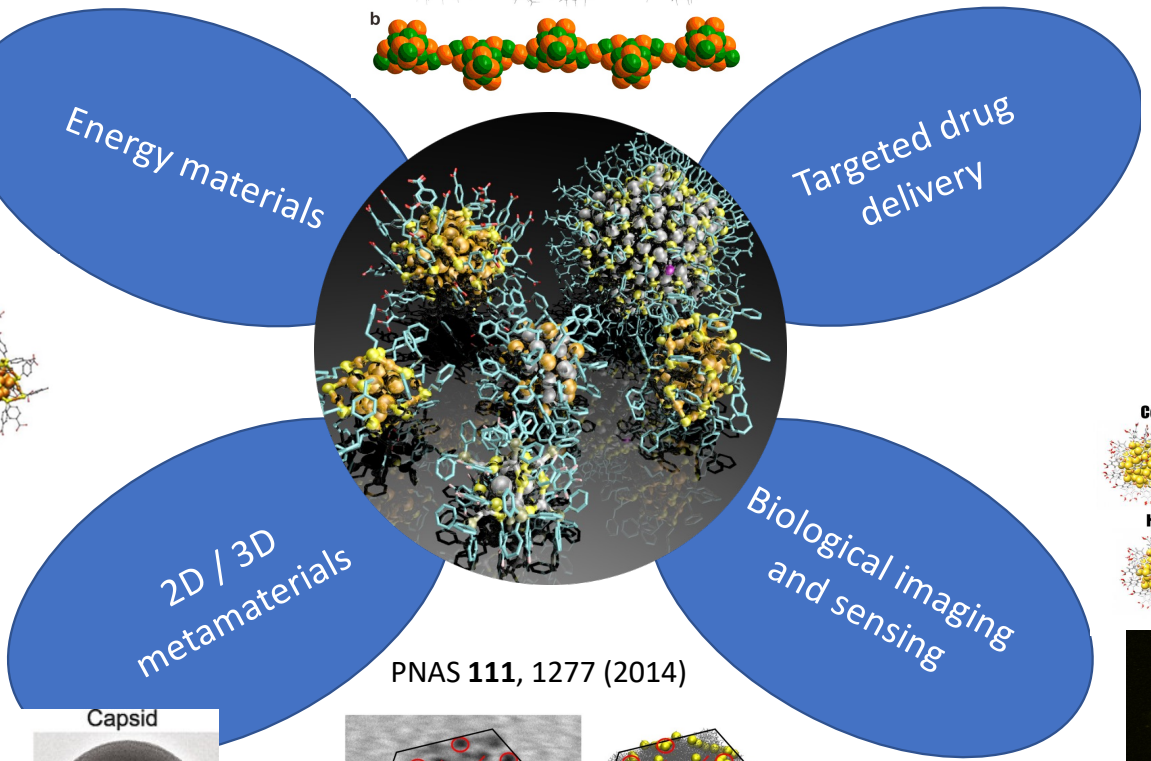


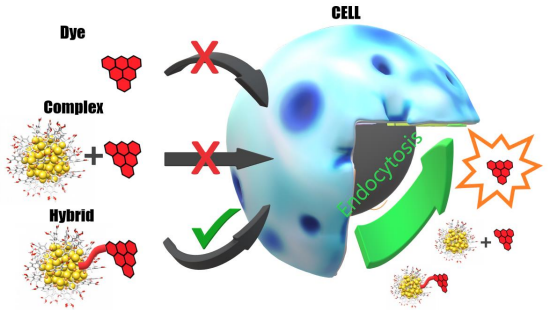
ACS Nanoscience Au (2021)



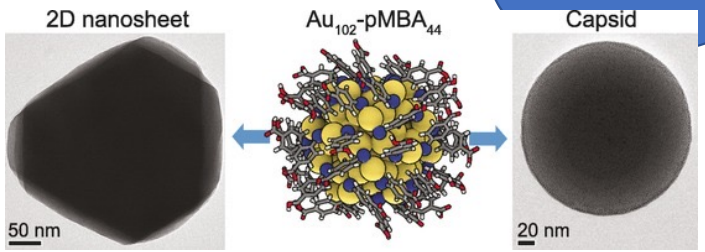
Colloidal crystal of Au25 clusters
Nature Chemistry
(2022, in print)



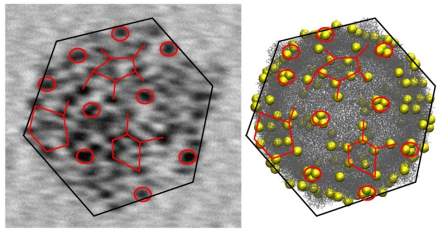




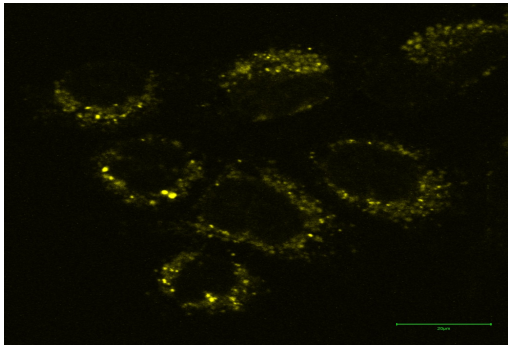
ACIE 55, 16035 (2017)



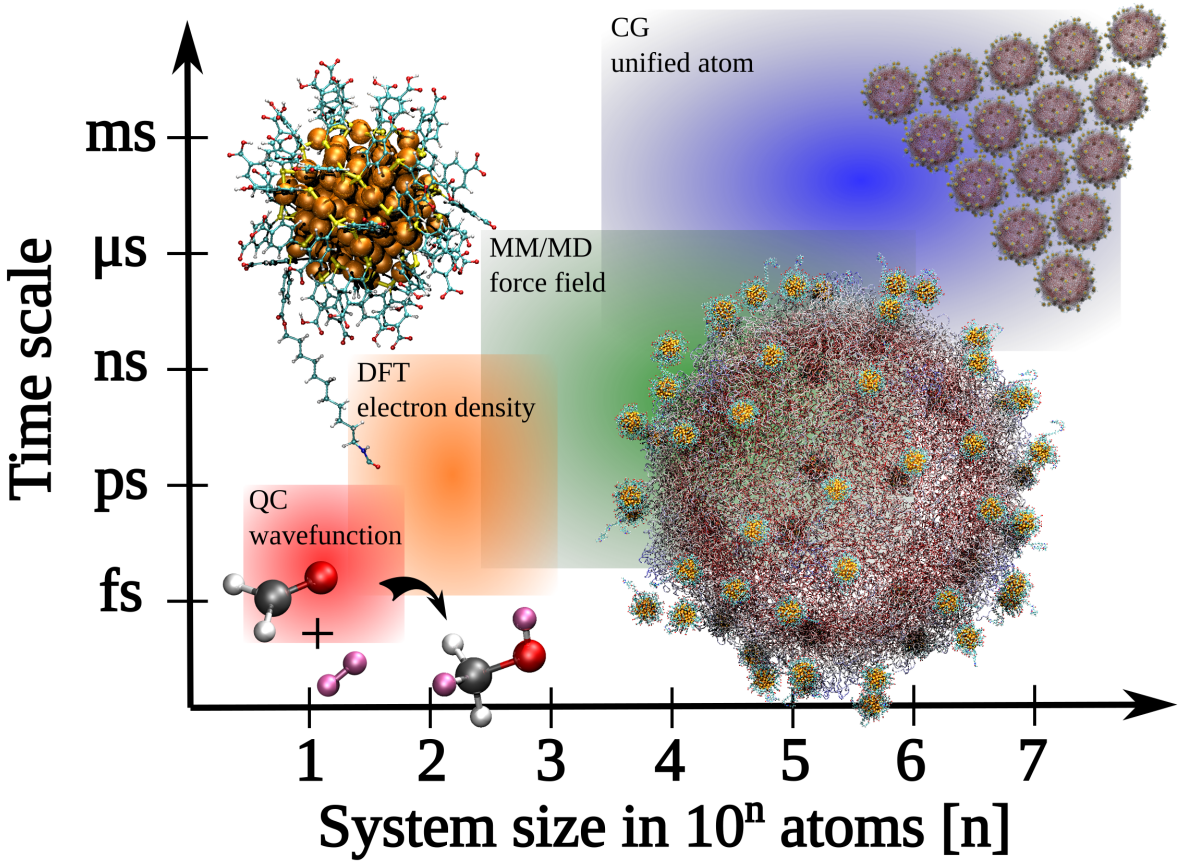
PNAS **111**, 1277 (2014)



Nanoscale Advances
2021, 2022



Multiple scales – multiple methods



On time scales:

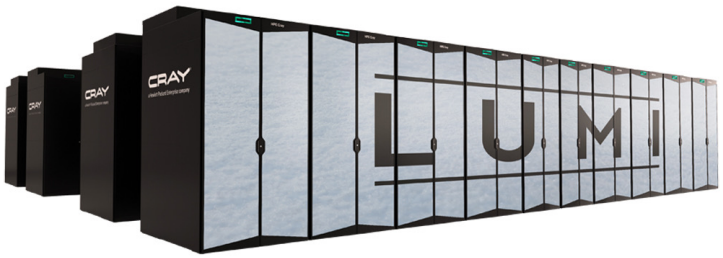
Folding of a protein – microsec to millisec

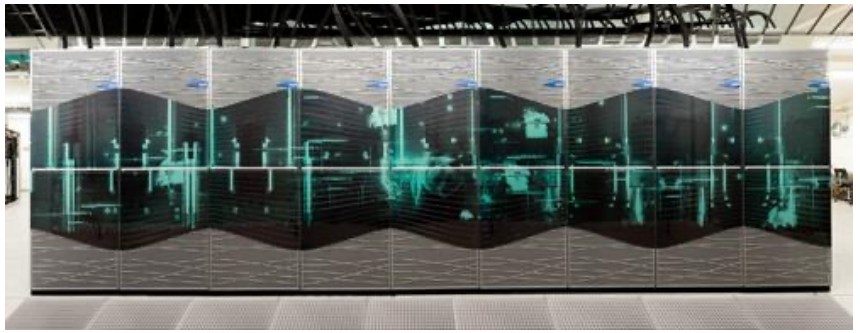
Self-diffusion over 1 micron in liquid at room temperature – millisec

In the future, machine learning **may** help to accelerate atomistic simulations (e.g. new efficient force fields allowing chemistry to happen) and bridge time- and length-scales, but **realizations to nanomaterials** are currently scarce and highly non-trivial

Malola and Häkkinen, Nature Comm **12**, 2197 (2021)

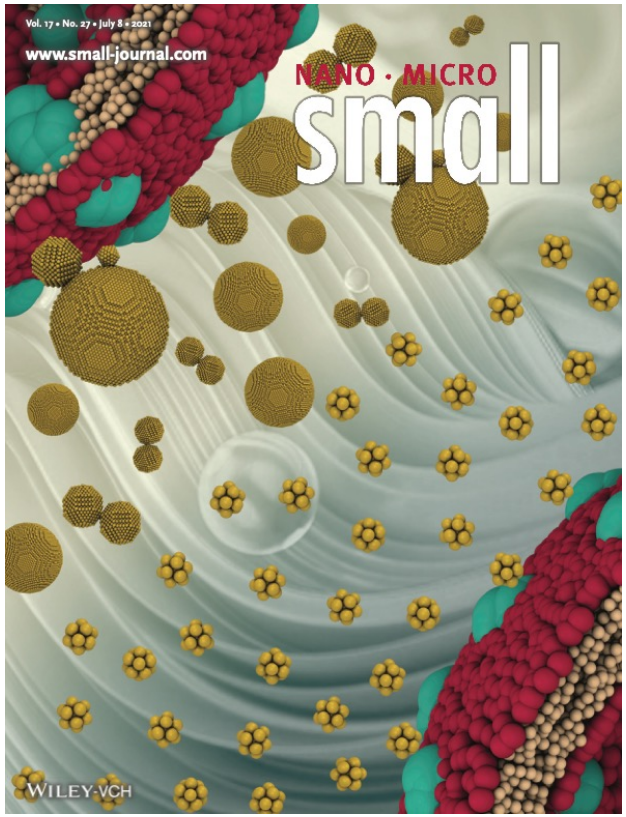
CSC

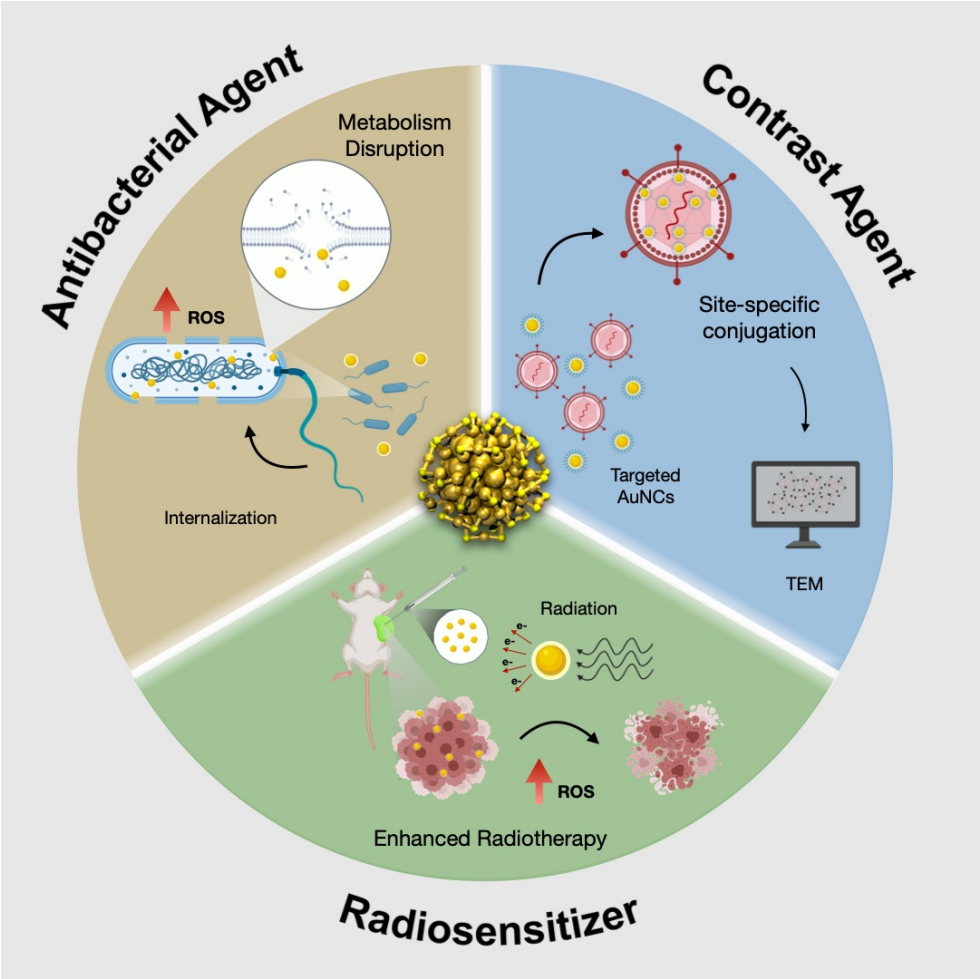




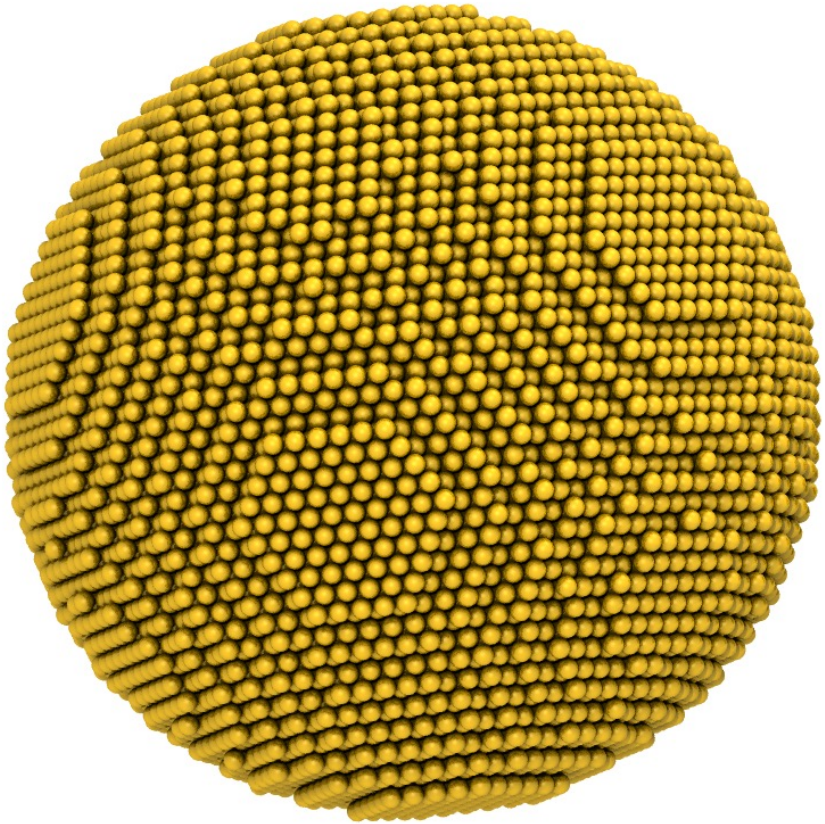
Targeted drug delivery

Current use of gold nanoclusters in biomedical applications



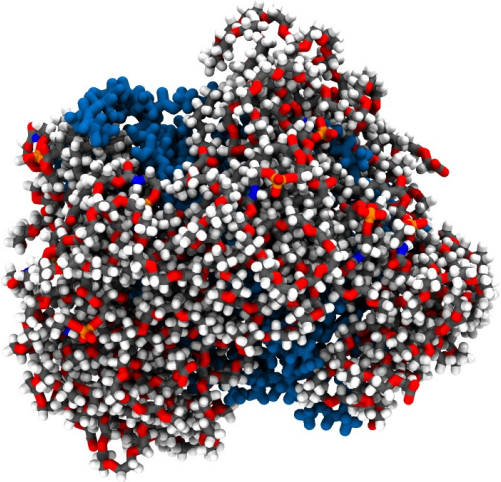


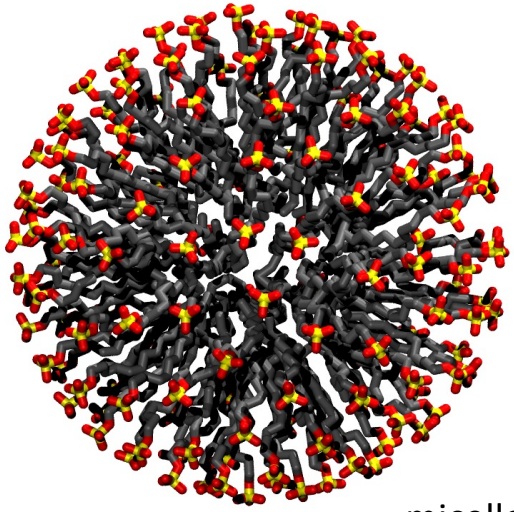
Matus, Häkkinen, Small 17, 2005499 (2021)



10 nm gold nanoparticle
5% variation in size
→ +/- **75 000** atoms

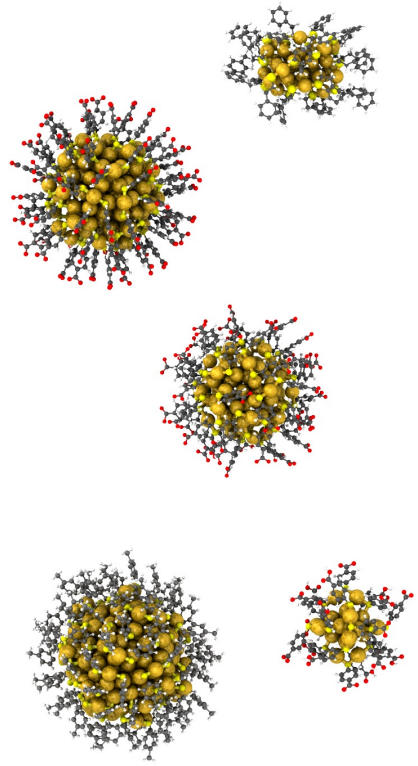
Polymer nanoparticle





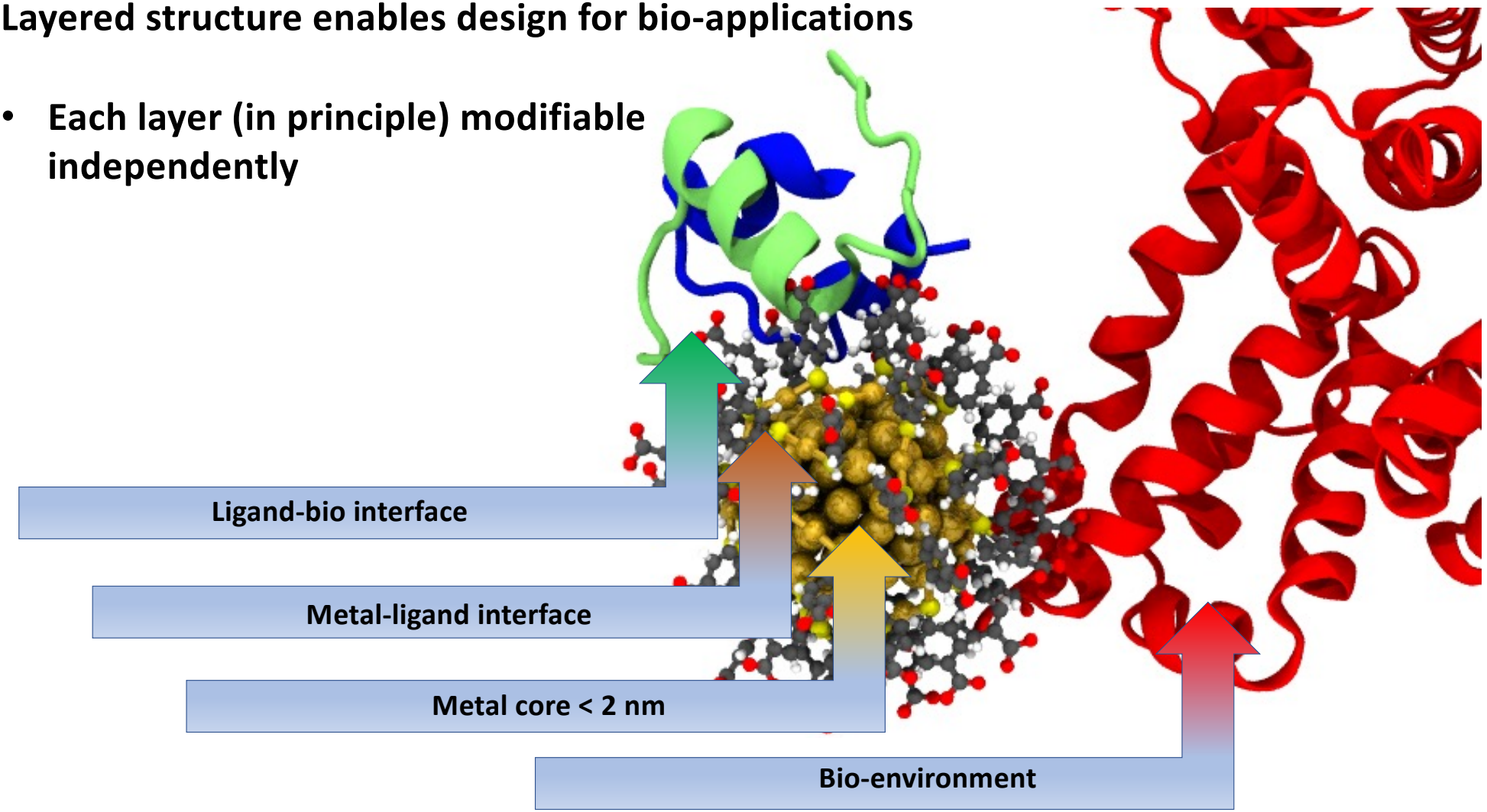
micelle

Atom-precise
Gold nanocluster
< 2 nm
Variation in size
+/- 0 atoms



Layered structure enables design for bio-applications

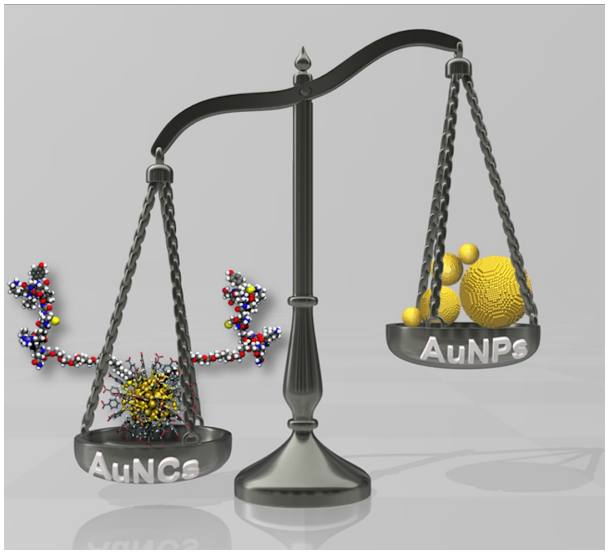
- Each layer (in principle) modifiable independently



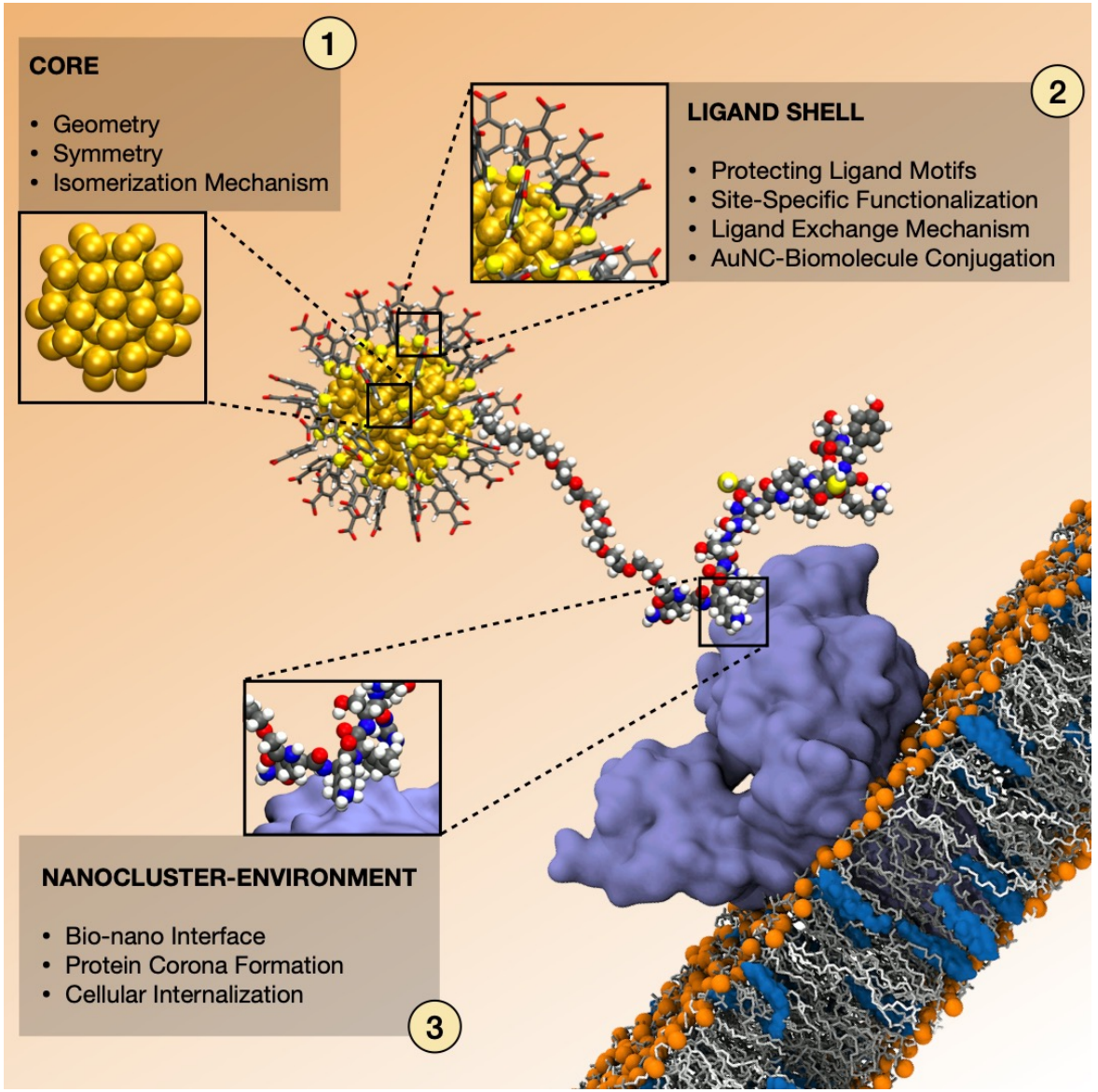
- **Nanoclusters: Many parameters for tuning functionality**

- **Atomistic simulations of nanoclusters offer unique tools for nanosystem design**

→ clusters "win" over nanoparticles



Matus, Häkkinen, Small 17, 2005499 (2021)



ACS NANOSCIENCE Au
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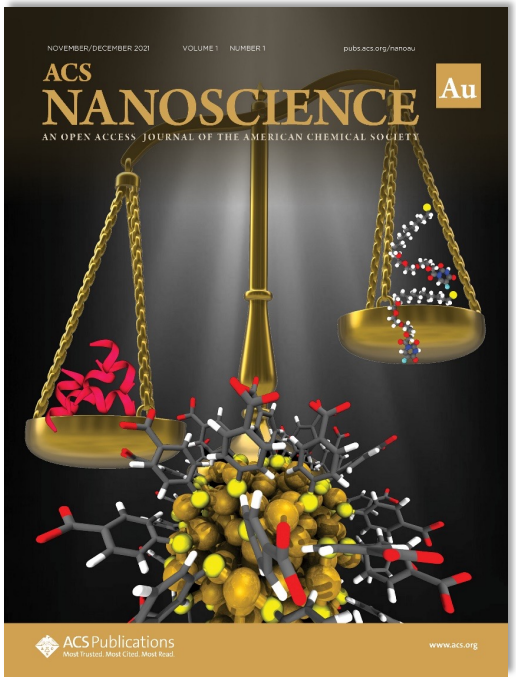
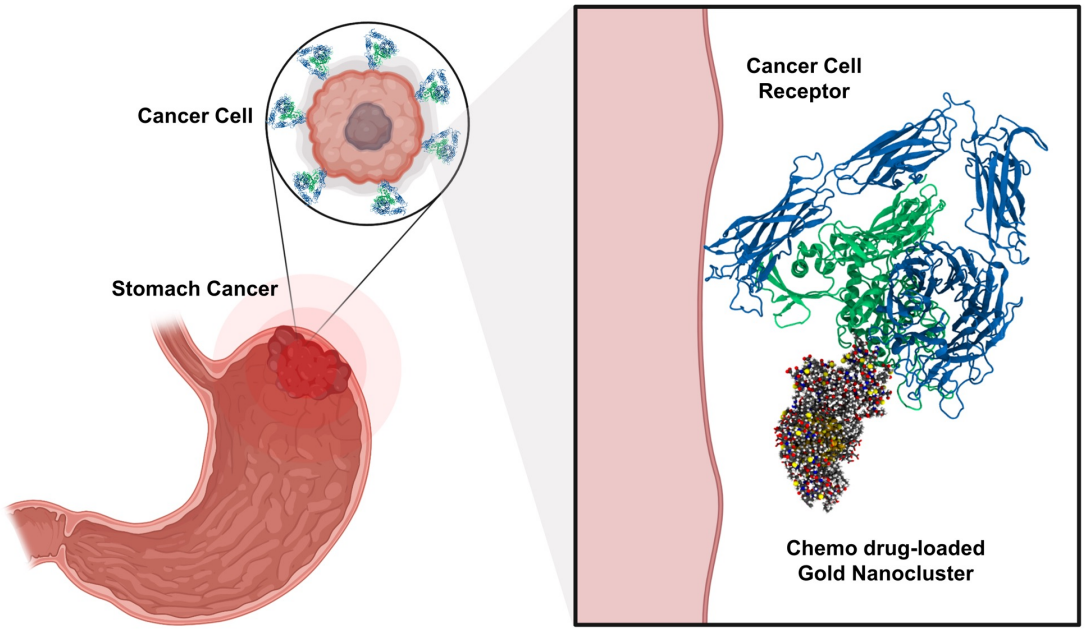
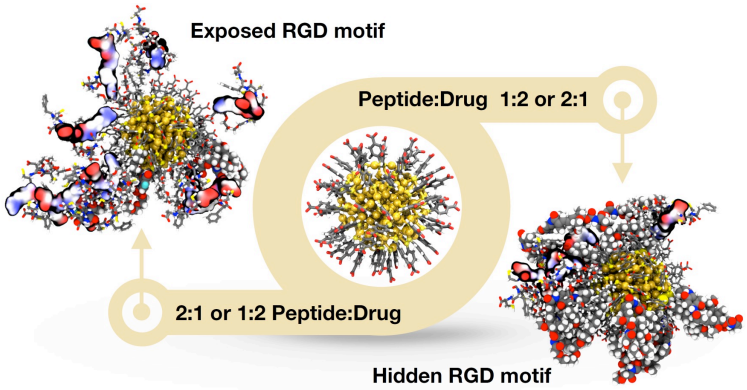
Ligand Ratio Plays a Critical Role in the Design of Optimal Multifunctional Gold Nanoclusters for Targeted Gastric Cancer Therapy

María Francisca Matus, Sami Malola, and Hannu Häkkinen*

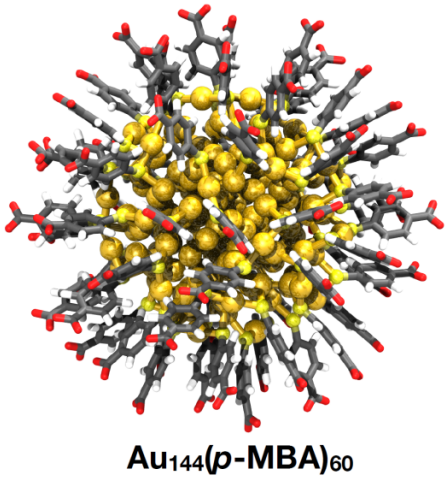
Cite This: https://doi.org/10.1021/acsnanoscienceau.1c00008 Read Online

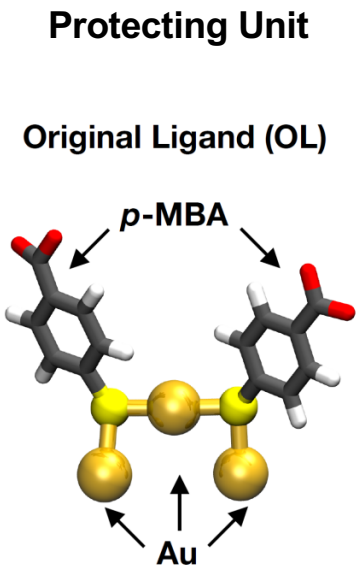


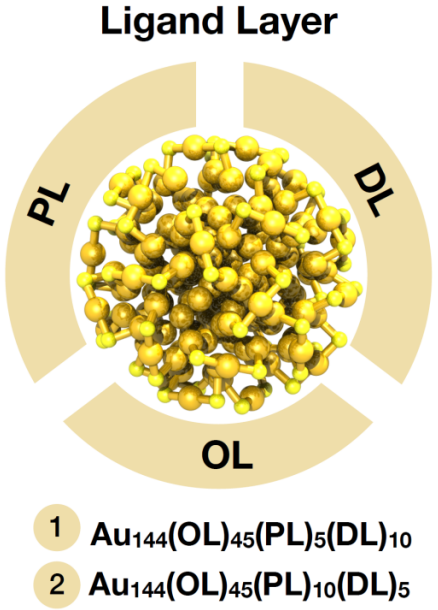




Multifunctional Nanoclusters based on $Au_{144}(p\text{-MBA})_{60}$

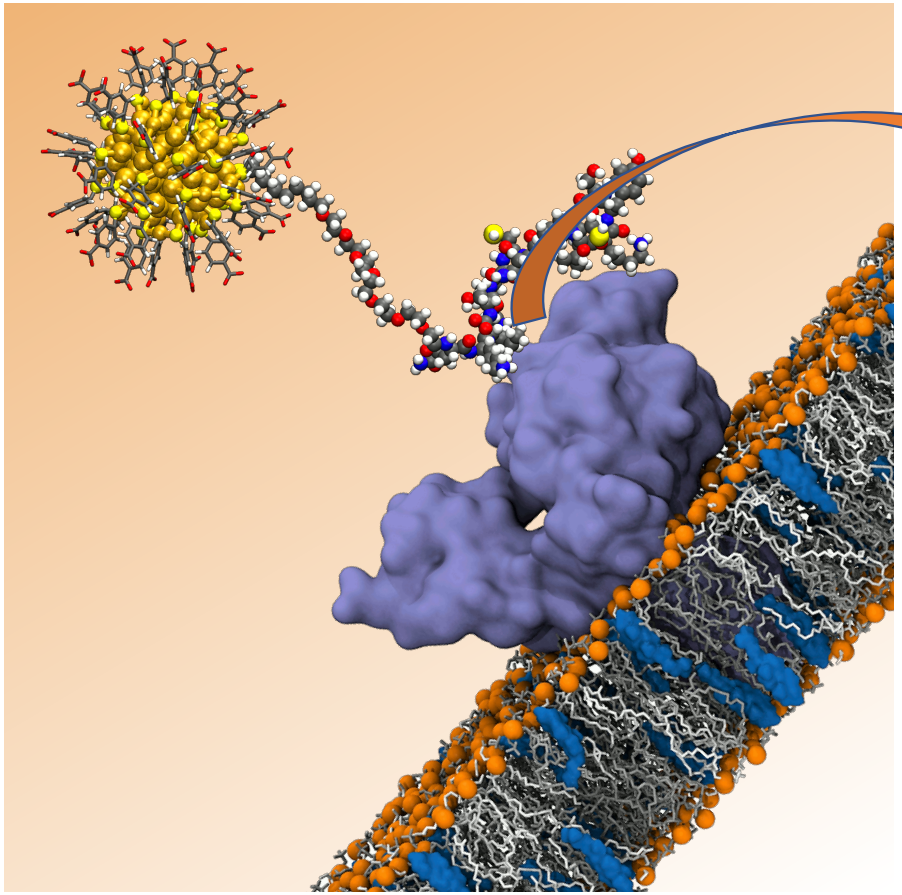






Schematic representation of the functionalization procedure of $Au_{144}(p\text{-MBA})_{60}$ nanocluster using two peptide:drug ratios (1:2 and 2:1).

Peptide selection from docking with extracellular part of αVβ3 integrin (out of 5 peptides)



Matus et al. ACS Nanoscience Au (2021)

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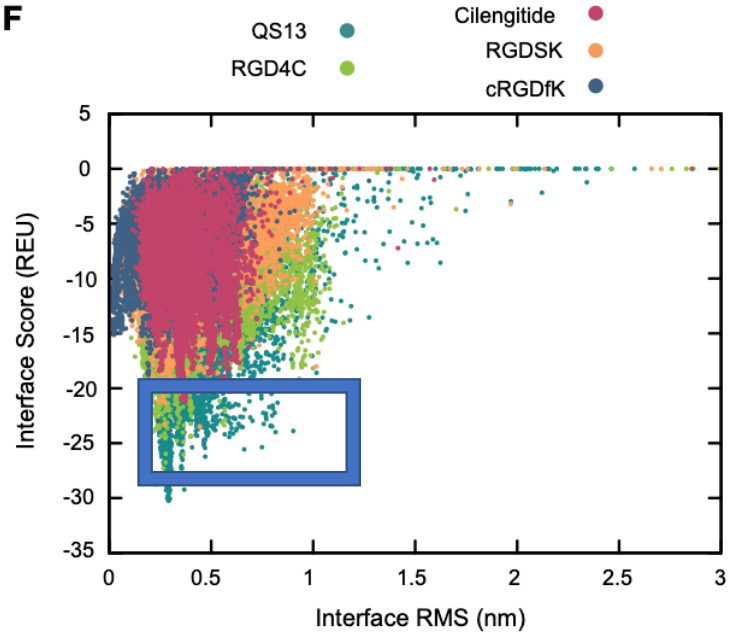
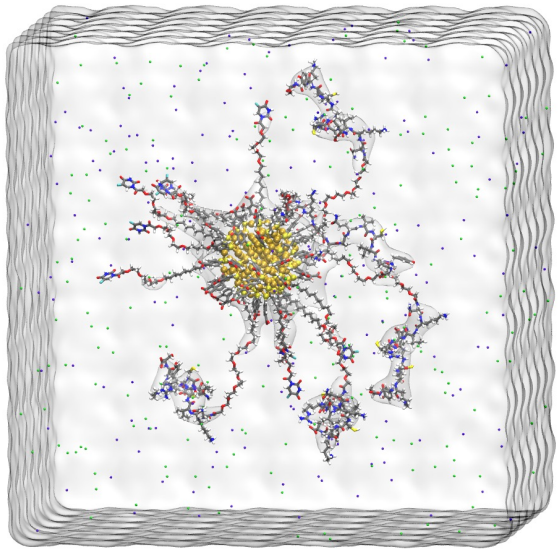


The "best" QS13 and RGD4C peptides combined with chemo drugs /inhibitors:

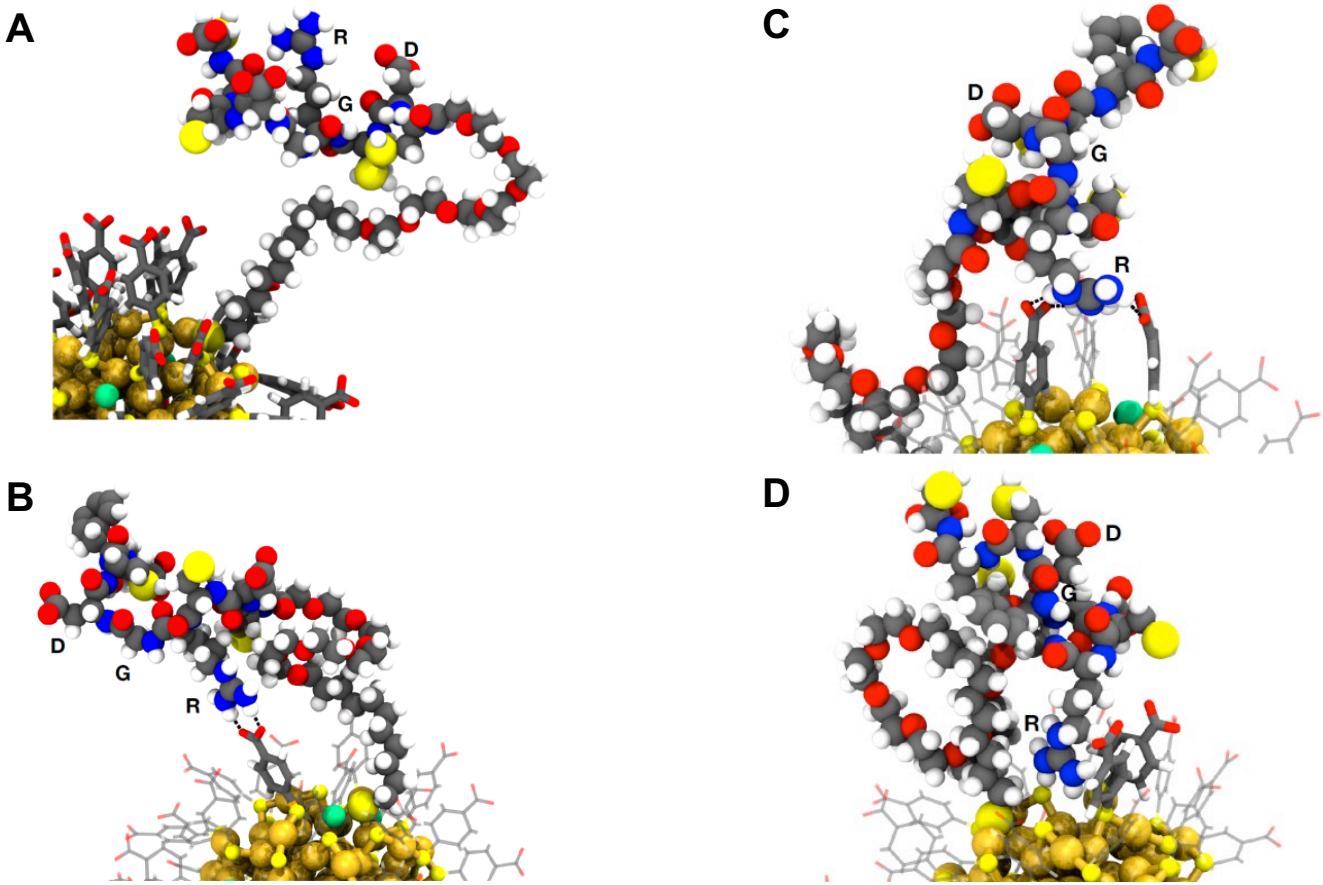
- EPI, 5FU, LIN, mTOR, TAN, TAS, CAP

60 ligands: 45 pMBA + peptide / drug
5/10 or 10/5
Peptides and drugs linked to gold via S-PEG (**in total: 28 systems)**

Targeting Motif Orientation



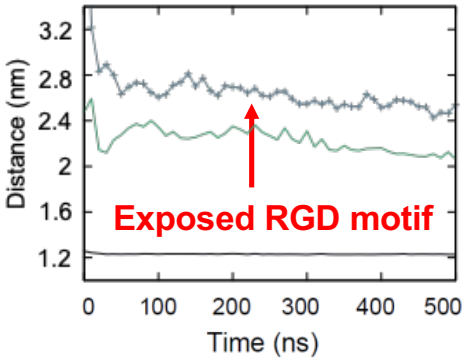
- Method: Classical MD Simulations
- Software: GROMACS
- 500-ns MD simulation at 310 K, 1 bar, wáter, fully deprotonated pMBAs

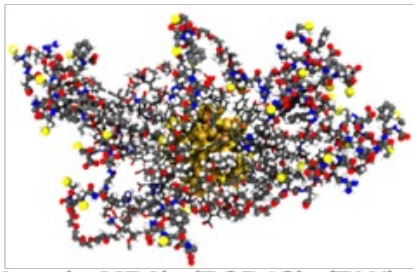


Representative cases of RGD motif orientation. Illustration when it is (A) completely or (B) relatively exposed to the solvent or when is (C, D) making contacts with the other components of the nanosystem (drugs are omitted for clarity).

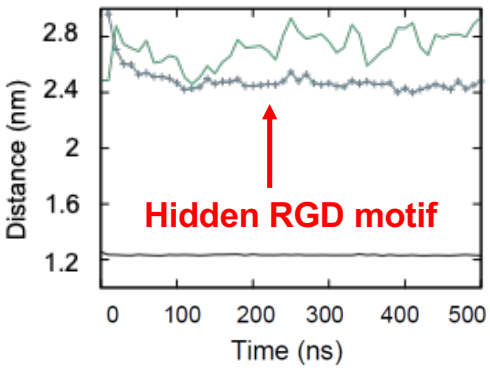
Ligand Ratio Dependency for Targeting Ability of Multifunctional AuNCs

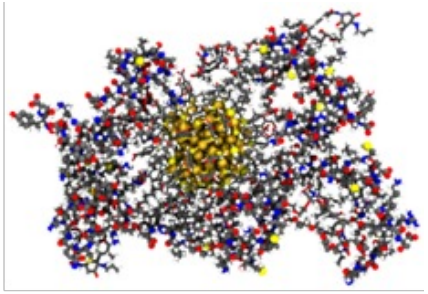
Peptide:Drug 2:1





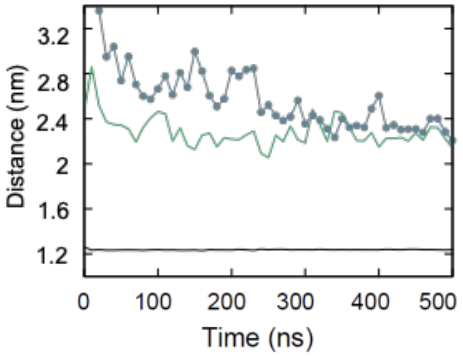
$Au_{144}(p\text{-MBA})_{45}(RGD4C)_{10}(TAN)_5$

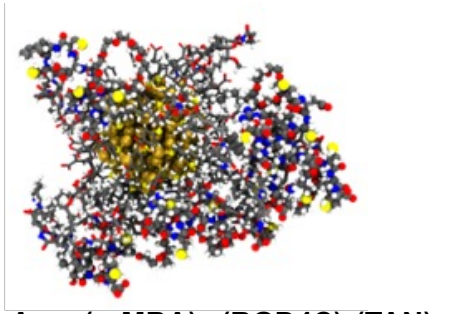




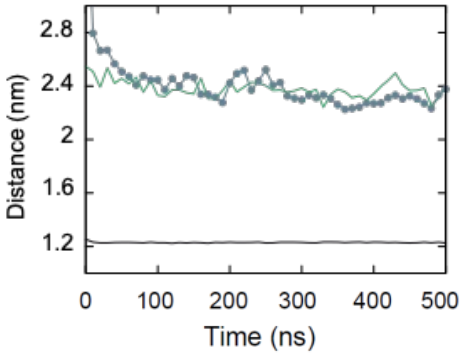
$Au_{144}(p\text{-MBA})_{45}(QS13)_{10}(TAN)_5$

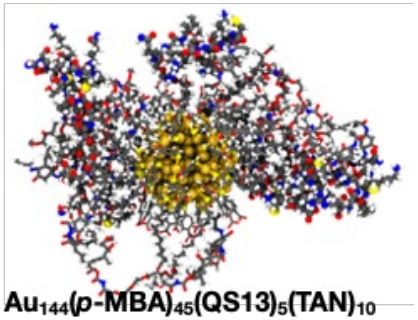
Peptide:Drug 1:2





$Au_{144}(p\text{-MBA})_{45}(RGD4C)_5(TAN)_{10}$





$Au_{144}(p\text{-MBA})_{45}(QS13)_5(TAN)_{10}$

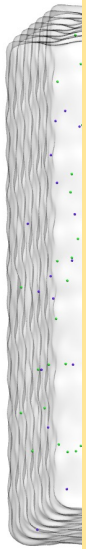
Drug 5x(Peptide) 10x(Peptide)

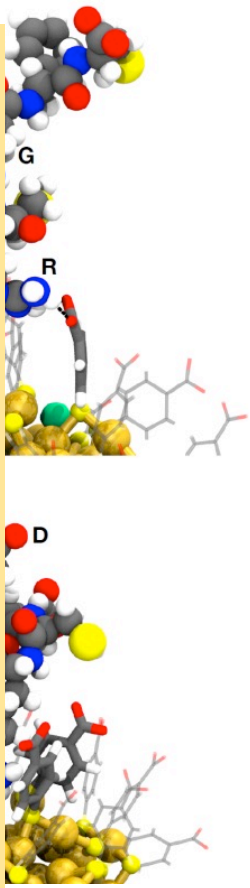
Distribution of the targeting motif of peptides on the ligand layer (representative cases).

Targeting Motif Orientation

OPTIMAL SYSTEMS (out of 28) HAVE:

- **Peptide layer well separate from thiol/drug layer**
- **Peptide recognition part visible to solvent**
- **Examples:**
  - **10 x QS13 / 5 x TOR**
  - **10 x RGD4C / 5 x 5FU**
  - **5 x RGD4C / 10 x TAS**



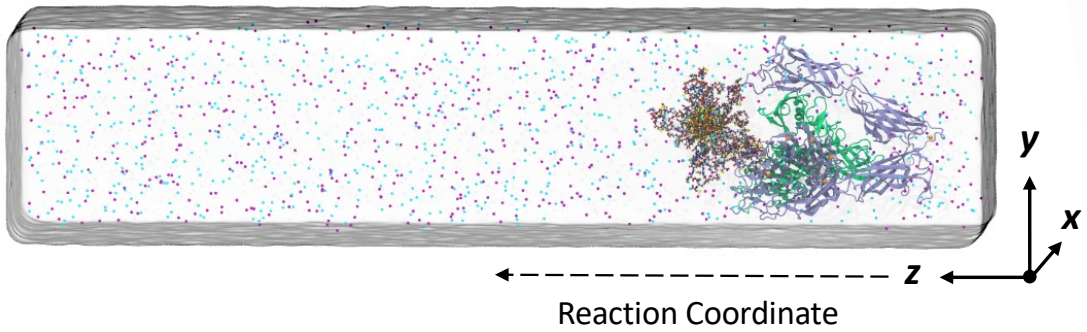


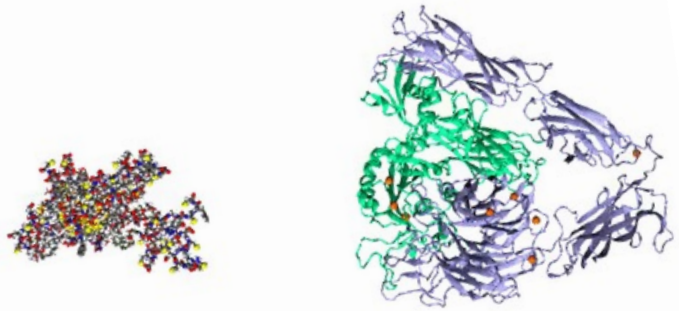
- Met
- Soft
- 500

wáter, fully deprotonated pMBAs

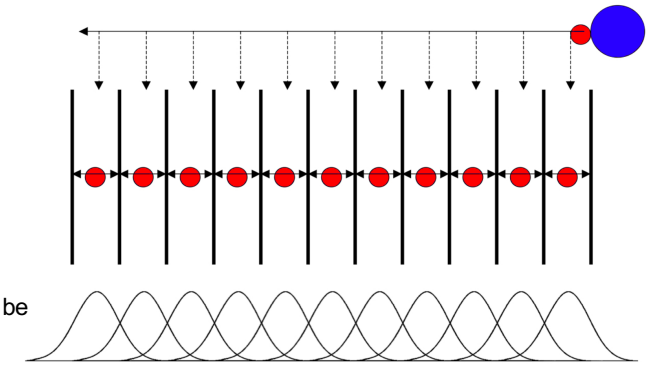
Representative cases of RGD motif orientation. Illustration when it is (A) completely or (B) relatively exposed to the solvent or when is (C, D) making contacts with the other components of the nanosystem (drugs are omitted for clarity).

Pulling MD and US Simulations





n configurations along the reaction coordinate are extracted:



Neighboring windows overlapping -> continuous energy function can later be derived

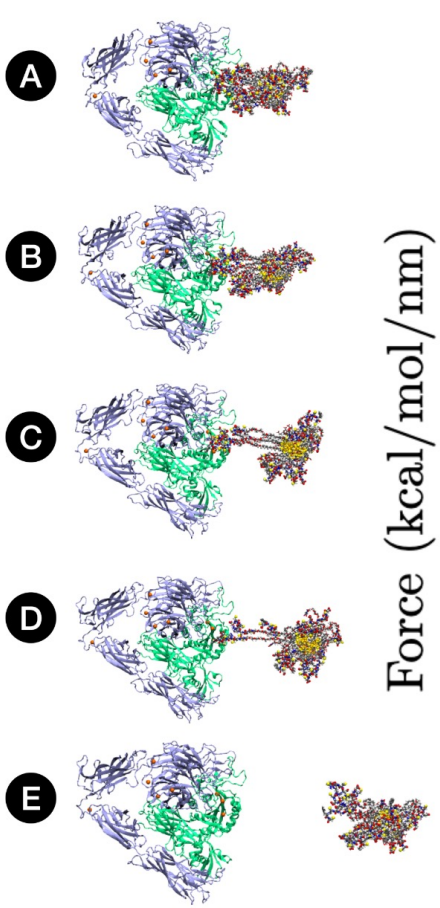
- 5-ns Pulling MD at 310 K, 1 bar
- > 650,000 atoms per (10) system

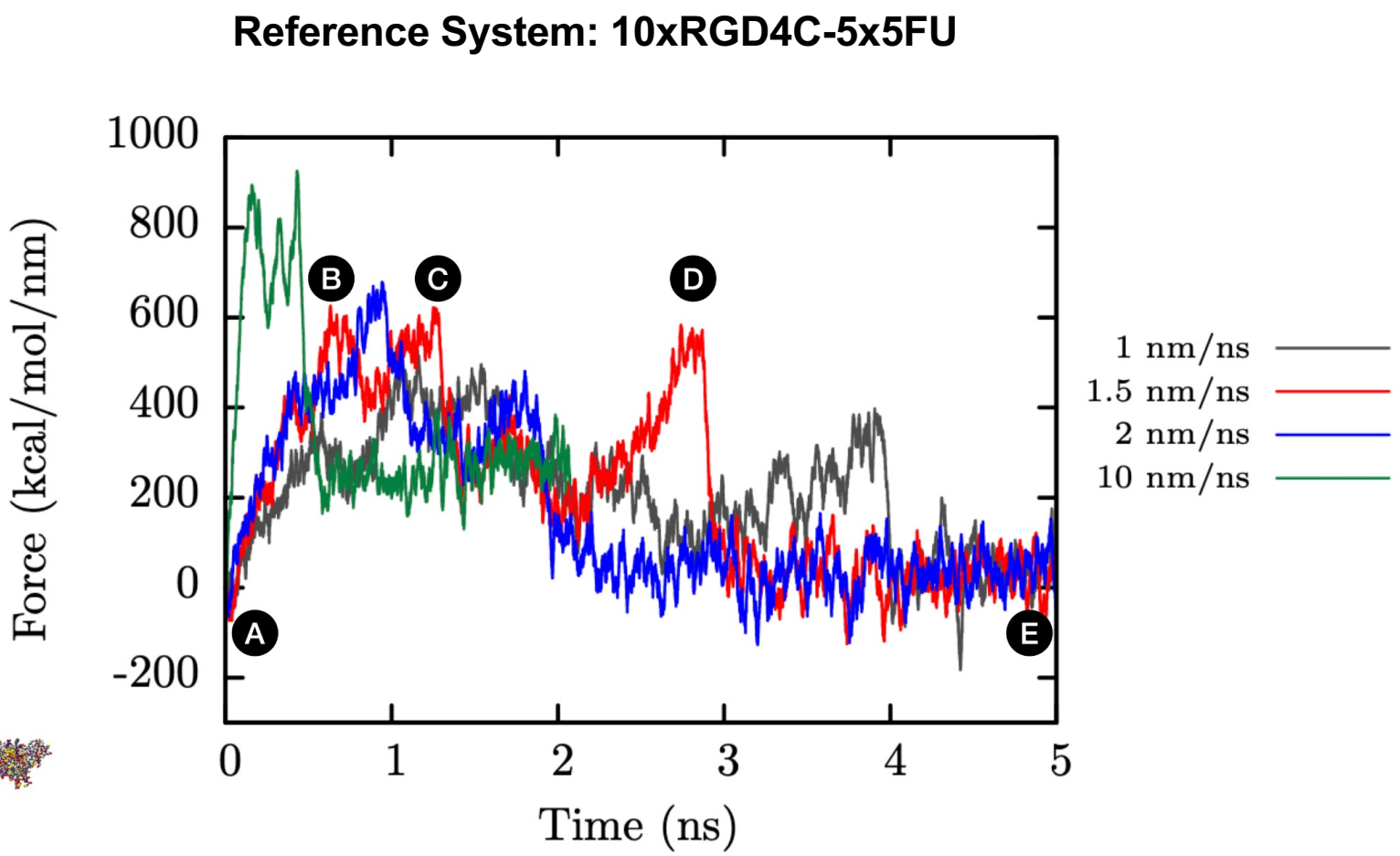
Umbrella sampling (US) simulations:

- > 30 US windows were extracted every 0.2 nm
- 10 ns or 80 ns US simulations were performed for each window (> 4 µs US simulations) to guarantee sampling convergence

J. Phys. Chem. B 2010, 114, 4, 1652−1660

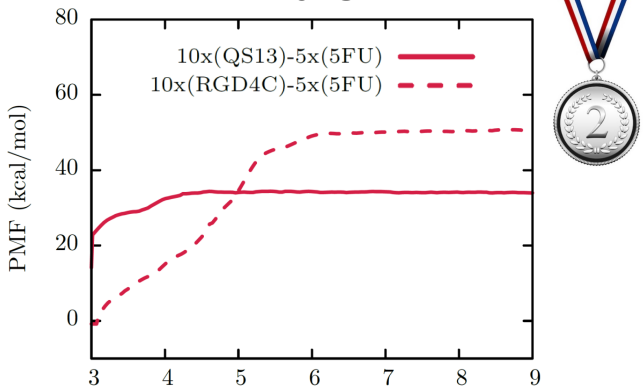
Dissociation Pathway



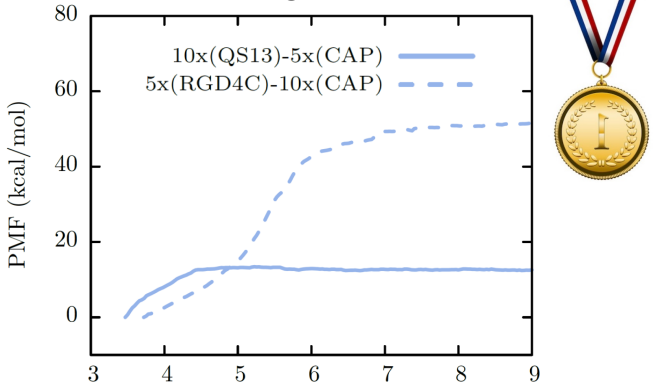


Best Combination of Peptide:Drug based on Binding Free Energy

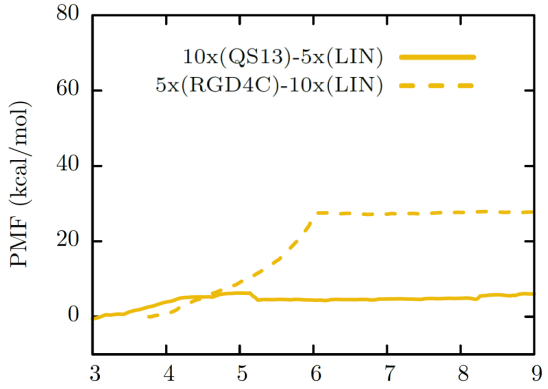
5FU



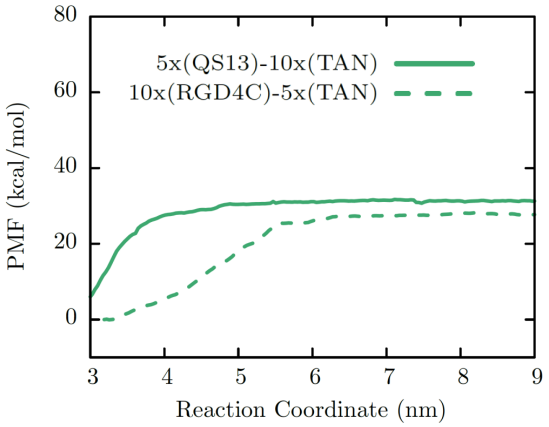
CAP



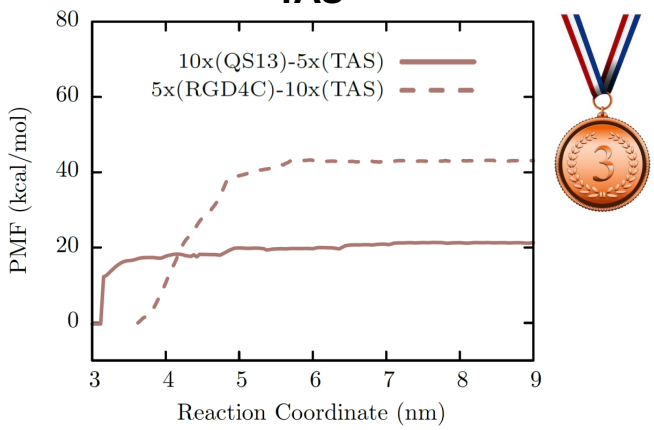
LIN



TAN



TAS



Final Set of Best Candidates:

1. 5x(RGD4C)-10x(CAP)
2. 10x(RGD4C)-5x(5FU)
3. 5x(RGD4C)-10x(TAS)
4. 5x(QS13)-10x(TAN)
5. 5x(RGD4C)-10x(LIN)

Ongoing and future work

- Simulations of the effects of biomolecular corona around the AuNC/peptide/drug particles
  (ongoing, expanding to use graph theory and machine learning to analyse AuNC / bio interface)

- Lab synthesis of the AuNCs with most promising peptide/drug combinations
  (ongoing, collaborations with labs in Singapore and France)

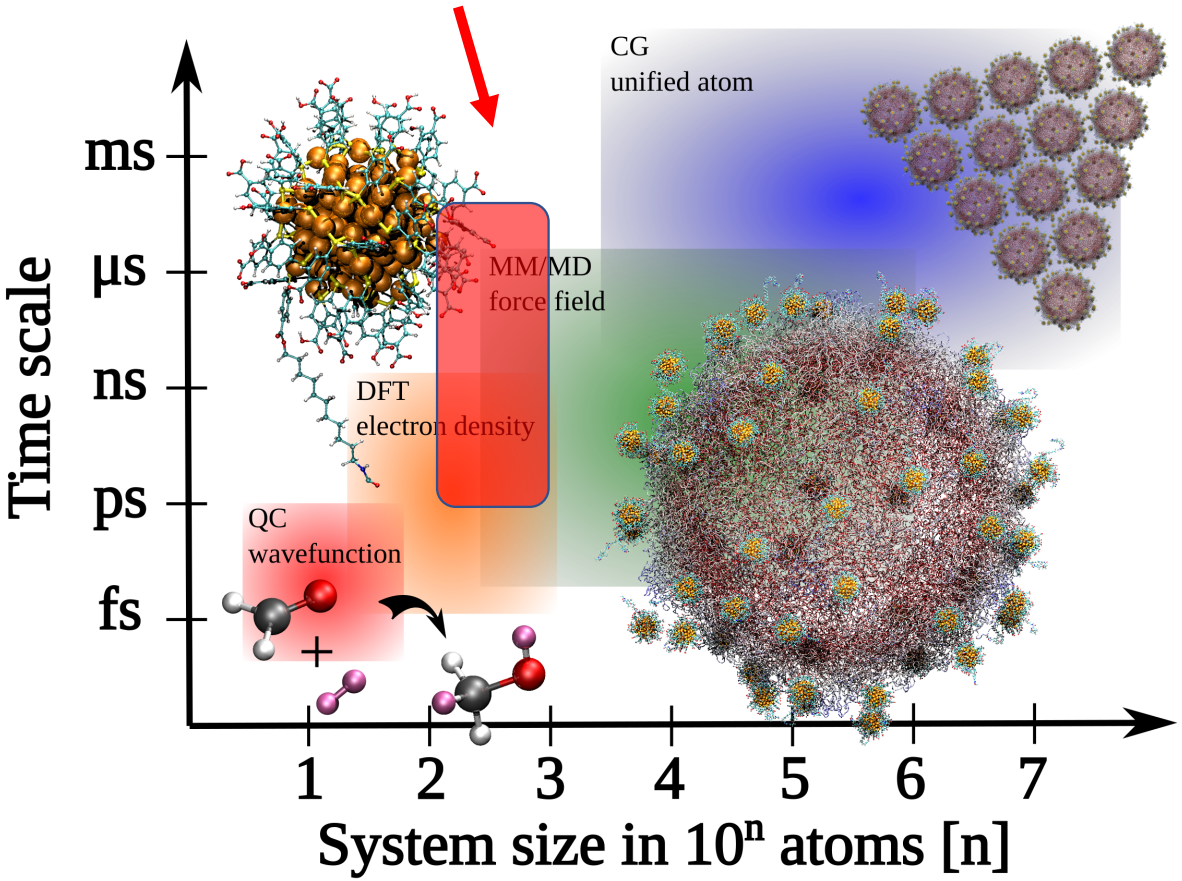
- Experiments on AuNC/peptide/drug particles exposed to human serum
  (collaboration within JYU Sports Science Faculty)

- Tests against cancer cell lines

- Mice models

Multiple scales – multiple methods

DFT-learned ML / MD ; Graph theory



Malola and Häkkinen, Nature Comm **12**, 2197 (2021)