Understanding the difference in ARMs-antibody interactions by docking and molecular dynamics

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INTRODUCTION

- **Antibody-recruiting molecules** (ARM)[1] are a promising class of molecules in the field of immunotherapy.
- Combination of **anchoring groups** (for target cell binding) and **haptens** (for antibody binding) to trigger response of **immune effector cells**.
- Aim: increase of the binding affinity by using multivalent ARM[2].

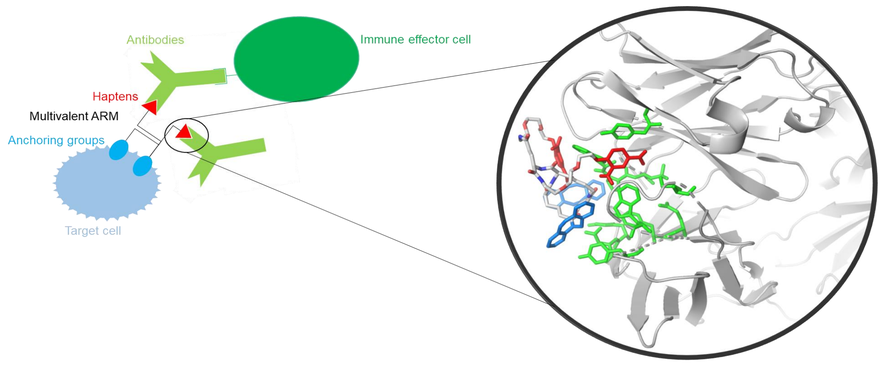
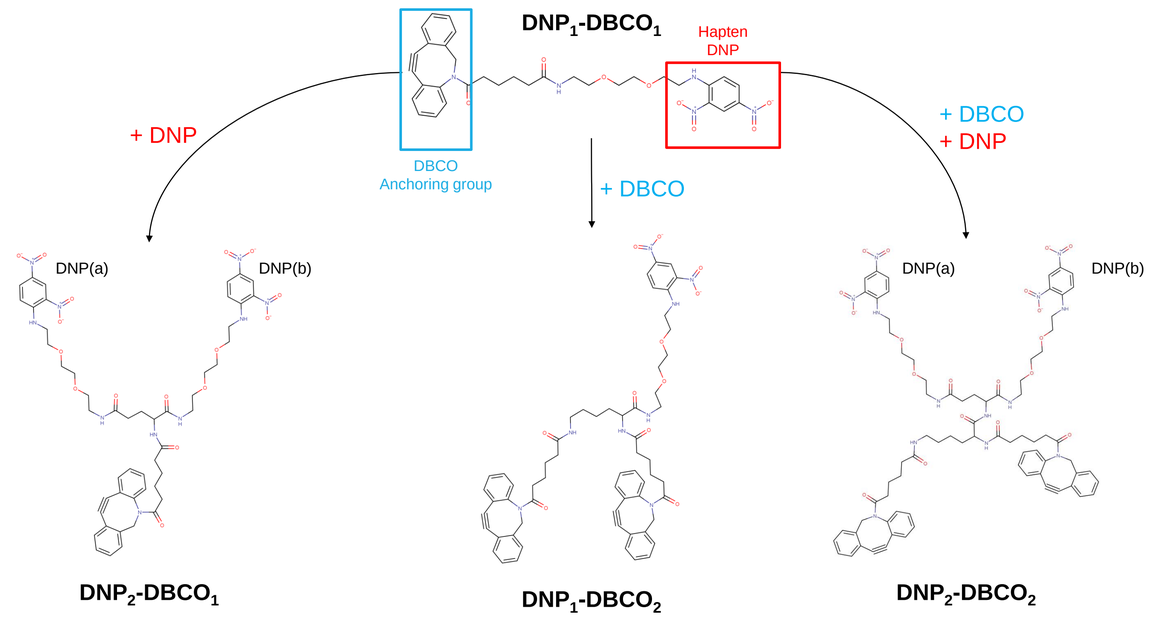
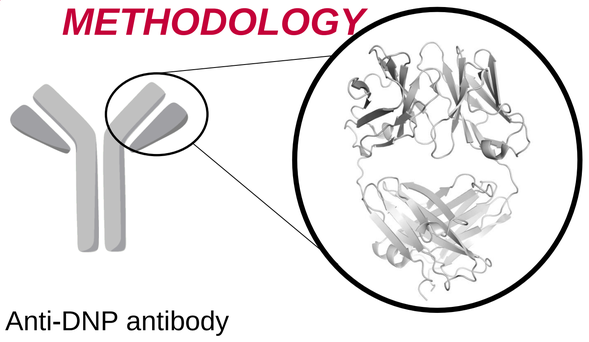


Figure 1: Sketch of the ARM-mediated immunotherapeutic approach.

- Modelling of 4 molecules with different number of haptens and anchoring groups.

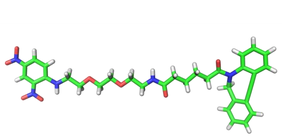


METHODOLOGY



Anti-DNP antibody

Fab fragment from Protein Data Bank
PDB ID : 1BAF



Docking
Flexible docking of the ARM on the Fab fragment with MedusaDock 2.0[3]

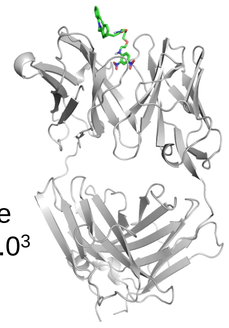


Figure 2a: Snapshot of the docked structure.

Molecular dynamics
250ns

- AM1-bcc charges
- GAFF2/AMBER16[4]
- Explicit water model (TIP3P)

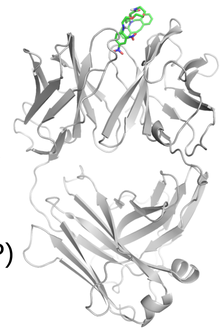


Figure 2b: Snapshot of MD at 250 ns.

Definition of the binding pocket

- Selection of the surrounding (distance cut-off : 5 Å) amino acids of the DNP ligand (green) in the 1BAF structure.
- 9 residues (in cyan) defined as the binding site.

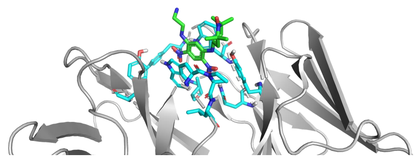


Figure 2c: 1BAF structure from Protein Data Bank.

RESULTS

Stability in the binding site

- Stability during MD assessed for each DNP by measuring distance between DNP and binding site.

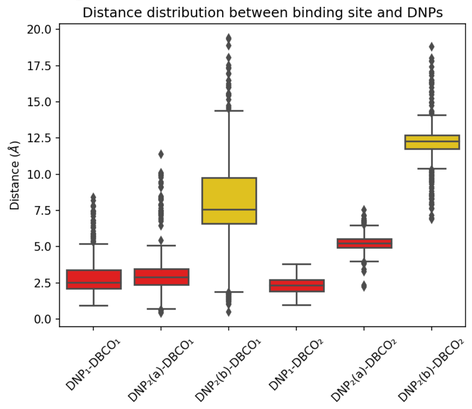


Figure 3: Boxplot distribution of distance between DNPs and binding site center of mass.

- DNP buried in the binding site for DNP_1-$DBCO_1$, DNP_2(a)-$DBCO_1$, DNP_1-$DBCO_2$ (median distance of 2.5 Å, 2.9 Å and 2.3 Å respectively).

Interactions of the DNPs

- Evaluation of the percentage of interactions (cut-off: 5 Å) between DNPs and each amino acids during MD.
- Comparision with the original 1BAF structure

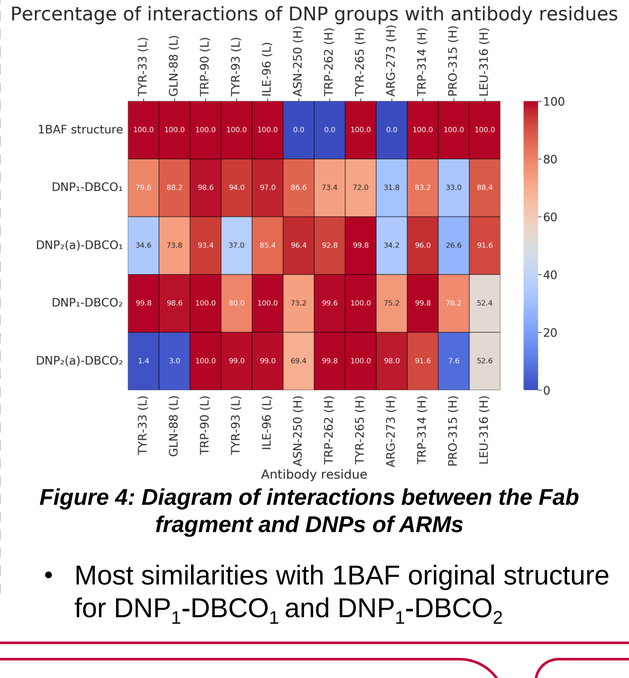


Figure 4: Diagram of interactions between the Fab fragment and DNPs of ARMs

- Most similarities with 1BAF original structure for DNP_1-$DBCO_1$ and DNP_1-$DBCO_2$

Similarities of interactions

- Importance of aromatic interactions in ligand-protein interaction process[5] → Lots of interactions with TYR (33,93,265) and with TRP (90,314).
- Stacking on both sides of DNP in 1BAF with TRP-90 and TRP-314 → Conservation of those interactions during the MD.

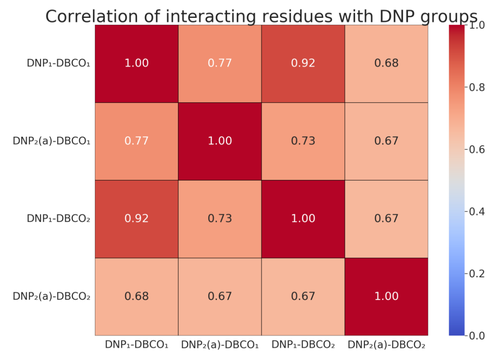


Figure 5: Correlation matrix of the interactions between antibody and DNPs

- High correlation coefficient (0.92) for monovalent ARMs → Similar binding modes.
- Poor correlation (0.67) for bivalent ARMs → Different binding modes.

Similarities of interactions

- Closeness of the DNPs in DNP_2-$DBCO_1$ → Interaction of the two DNPs with the same residues of the binding site (monotopic binding).
- Good separation of DNPs in DNP_2-$DBCO_2$ → Interaction with different residues (bitopic binding).

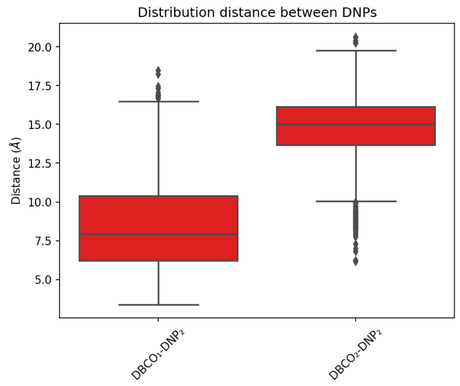


Figure 6: Boxplot distribution of distance between DNPs

CONCLUSION AND PERSPECTIVES

- The molecular modelling approach allows us to get insight on the conformation and the binding modes of mono an bivalent antibody-recruiting molecules.
- Understanding the difference in the binding modes could help the design of new ARMs to improve the immunotherapeutic effect.
- Avidity measurements and antibody recruitments have been measured experimentally to confirm the computational predictions.

ACKNOWLEDGMENTS

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