Chiral mismatch in collagen-mimetic peptides modulates cell migration through integrin-mediated molecular recognition

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Introduction

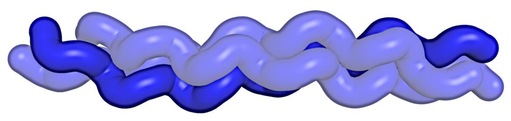
Does chirality influence cell-matrix interactions and cell migration?

- Engineering of three **surfaces coated with collagen or collagen-mimetic peptides (CMPs)**
- **Collagen** = major component of extracellular matrix (ECM)
- **Homochiral CMP** = full L-amino acids
- **Heterochiral CMP** = L- and D-amino acids → **Chiral mismatch!**

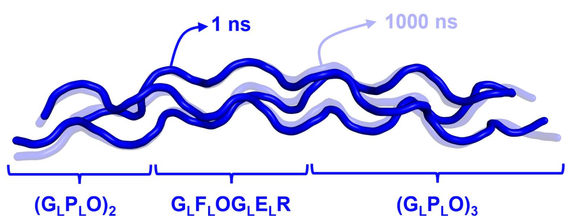
NATURAL COLLAGEN TYPE I

Single-chain = left-handed helix

Assembly into right-handed triple helix

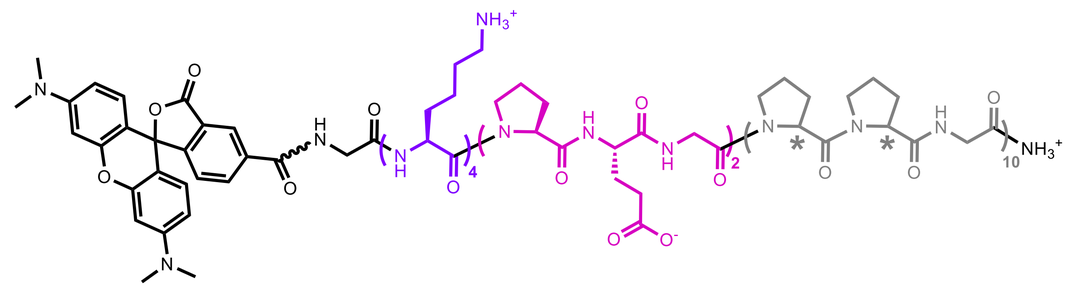


Natural collagen type I (Simplified model)

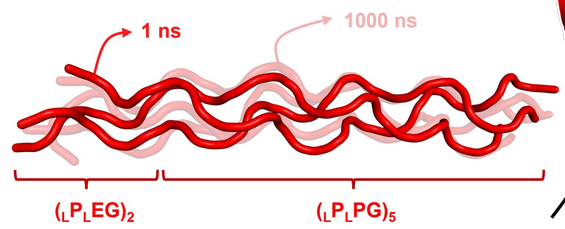


COLLAGEN-MIMETIC PEPTIDES (CMPs)

TAMRA-Gly-$(Lys)_4$-$(Pro\text{-}Glu\text{-}Gly)_2$-$(Pro^*\text{-}Pro^*\text{-}Gly)_{10}$

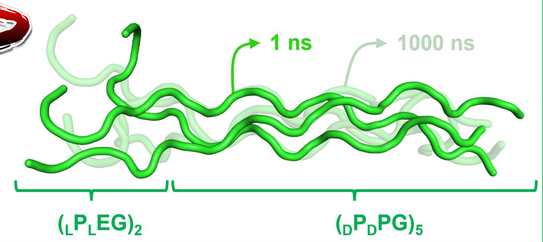


Homochiral CMP (Simplified model)



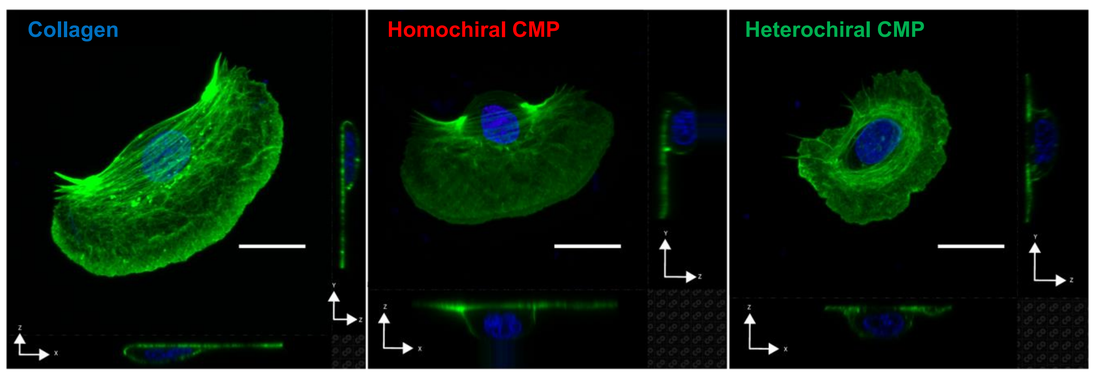
VS

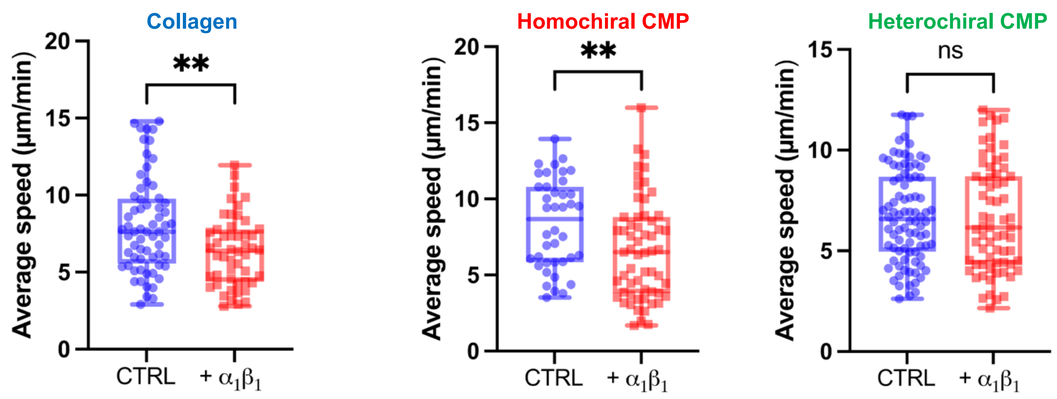
Heterochiral CMP (Simplified model)



Experimental findings

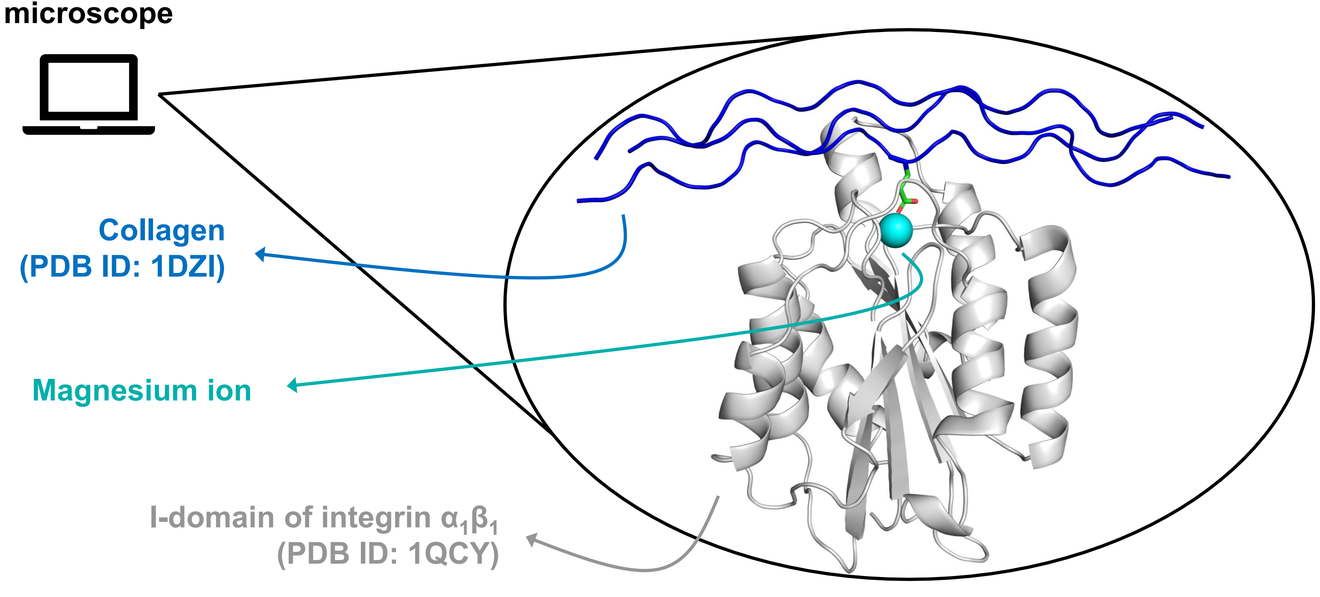
By Alexandre Remson





- Surface chirality impacts cell morphology, adhesion and migration
- Inhibiting integrin $\alpha_1\beta_1$ affects cell migration on **collagen** and **homochiral CMP** but NOT on **heterochiral CMP**

Investigation at the atomic scale – Molecular modeling



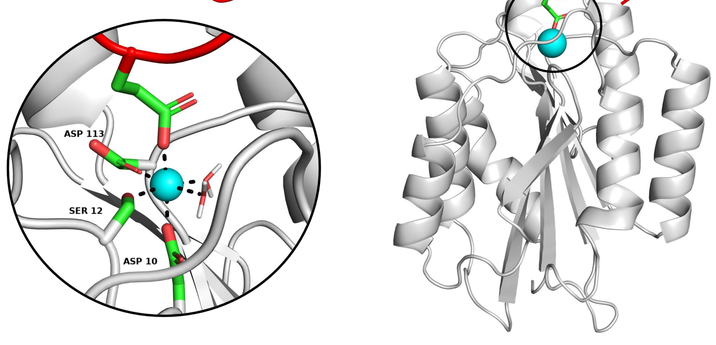
- Integrins = transmembrane proteins mediating adhesions between cells and ECM
- **I-domain of integrin $\alpha_1\beta_1$** = **collagen** recognition site: binding through « GFOGER » motif[1]
- Coordination of **Mg^{2+} ion** by glutamate

Simulation methodology

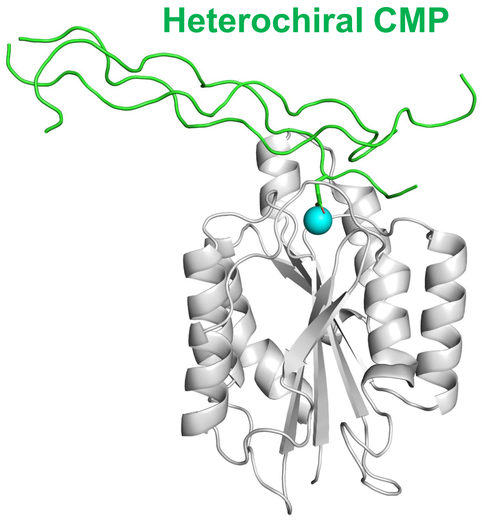
- **AMBER** suite of programs[2]
- **ff19SB** force-field[3]
- Explicit solvation (OPC water + 0.15 M NaCl)
- Microsecond timescale
- Five independant replicas for each system

Snapshots from the simulations

Homochiral CMP

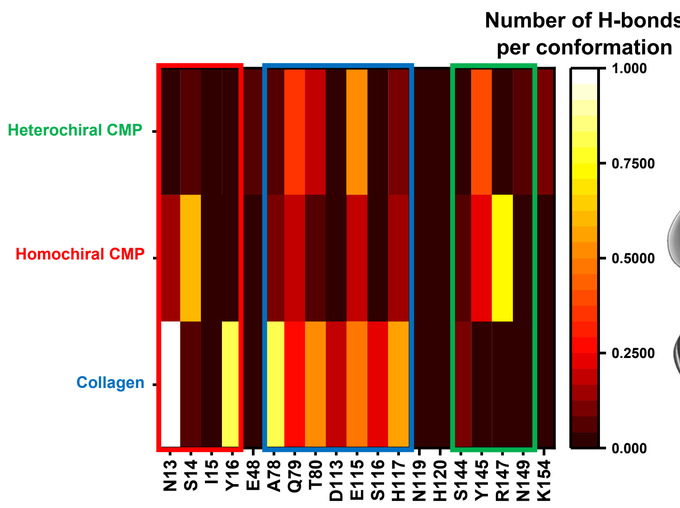


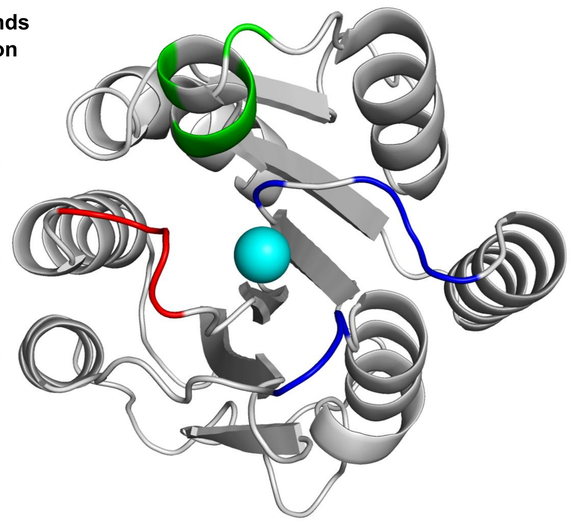
Heterochiral CMP



- Both CMPs are able to interact with the integrin through glutamate – Mg^{2+} coordination
- **Heterochiral CMP** is **disordered at the junction between L- and D-amino acids**

Hydrogen bonds in the binding site





- More interactions in the binding site for **homochiral CMP** than **heterochiral CMP**: **the chiral mismatch hinders the peptide – integrin recognition**

References

1. Knight, C. G. *et al.*, *J. Biol. Chem.* **2000**, *275*, 35–40. **2.** Case, D. A. *et al.*, *J. Comput. Chem.* **2000**, *26*, 1668–1688. **3.** Tian, C. *et al.*, *J. Chem. Theory Comput.* **2019**, *16*, 528–552.

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