Computational insights into the activation of PI3Kα by calmodulin (CaM) through c/nSH2 domains in p85α regulatory subunit: Implication for CaM-PI3K crosstalk in K-Ras-driven cancer
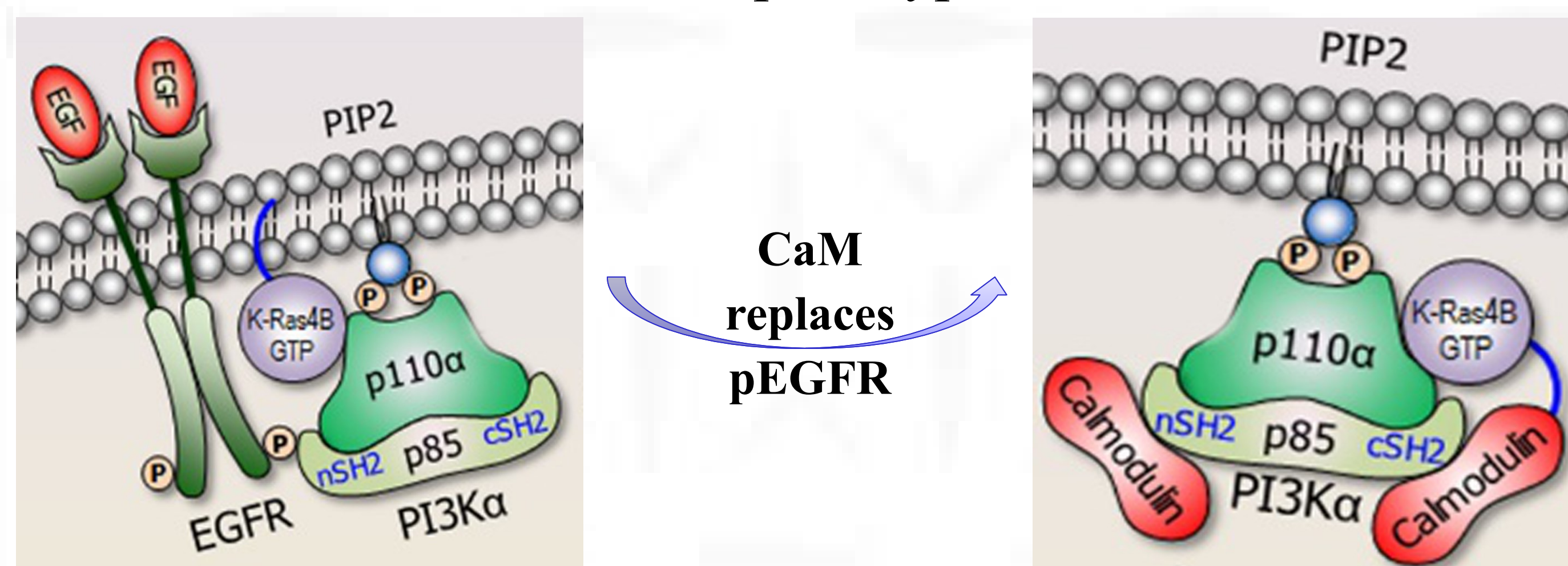
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Keywords: Calmodulin; PI3Kα; K-Ras4B; Molecular Dynamics simulations; Protein-Protein interactions

Introduction

- K-Ras mutations lead to 30% oncogenesis.
- CaM-PI3K crosstalk is critical to K-Ras-driven cancer.
- CaM replaces pEGFR to abnormally activate PI3Kα.
- K-Ras4B/CaM/PI3Kα complex hypothesis in carcinoma.
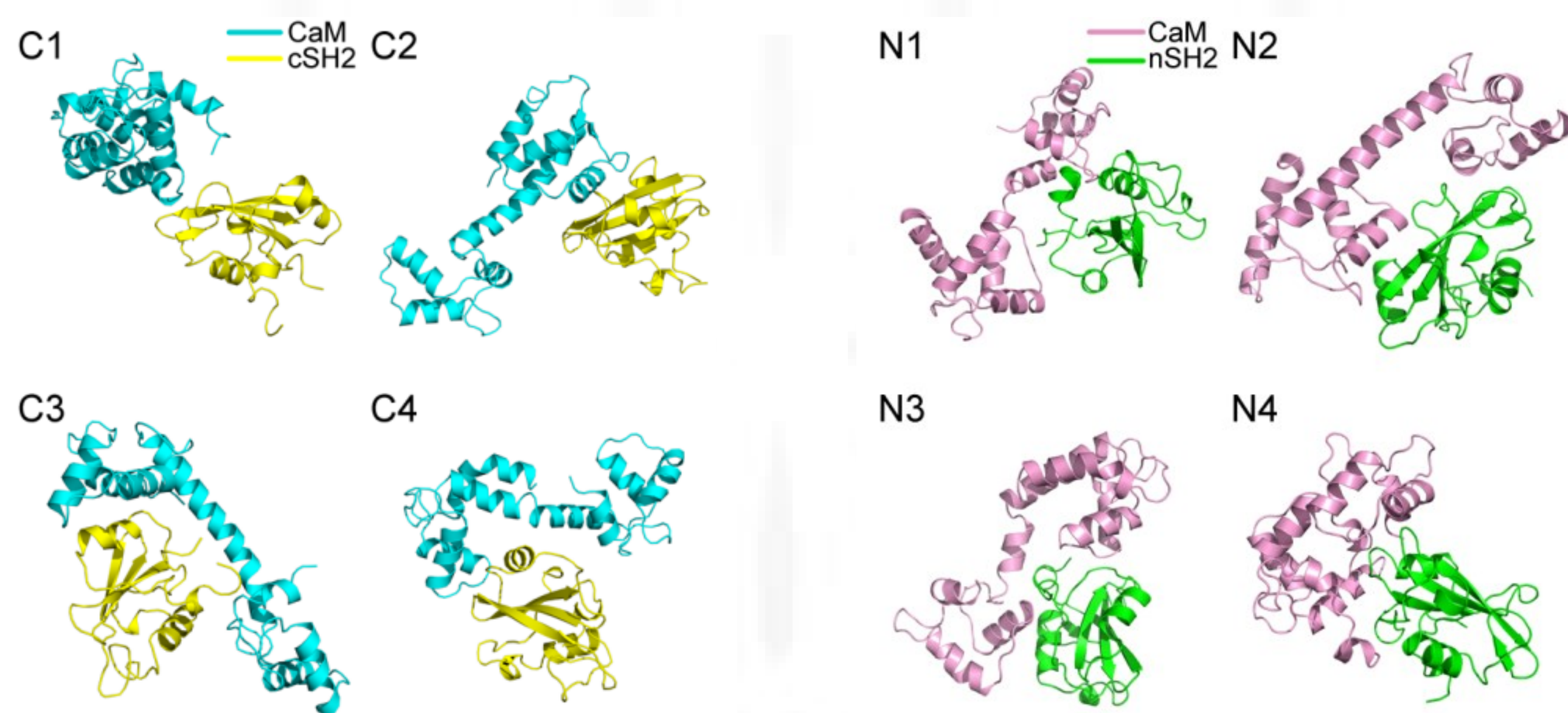

Methods

- ☐ Molecular Dynamics (MD) simulations
- ☐ Molecular Mechanics Generalized Born Surface Area (MM/GBSA) calculations
- ☐ Proteins, Interfaces, Structures and Assemblies (PISA) analysis

Results

Simulation Systems Construction

➤ Top eight results (C1-C4/N1-N4) predicted by PRISM and pEGFR-c/nSH2 structures from PDB.
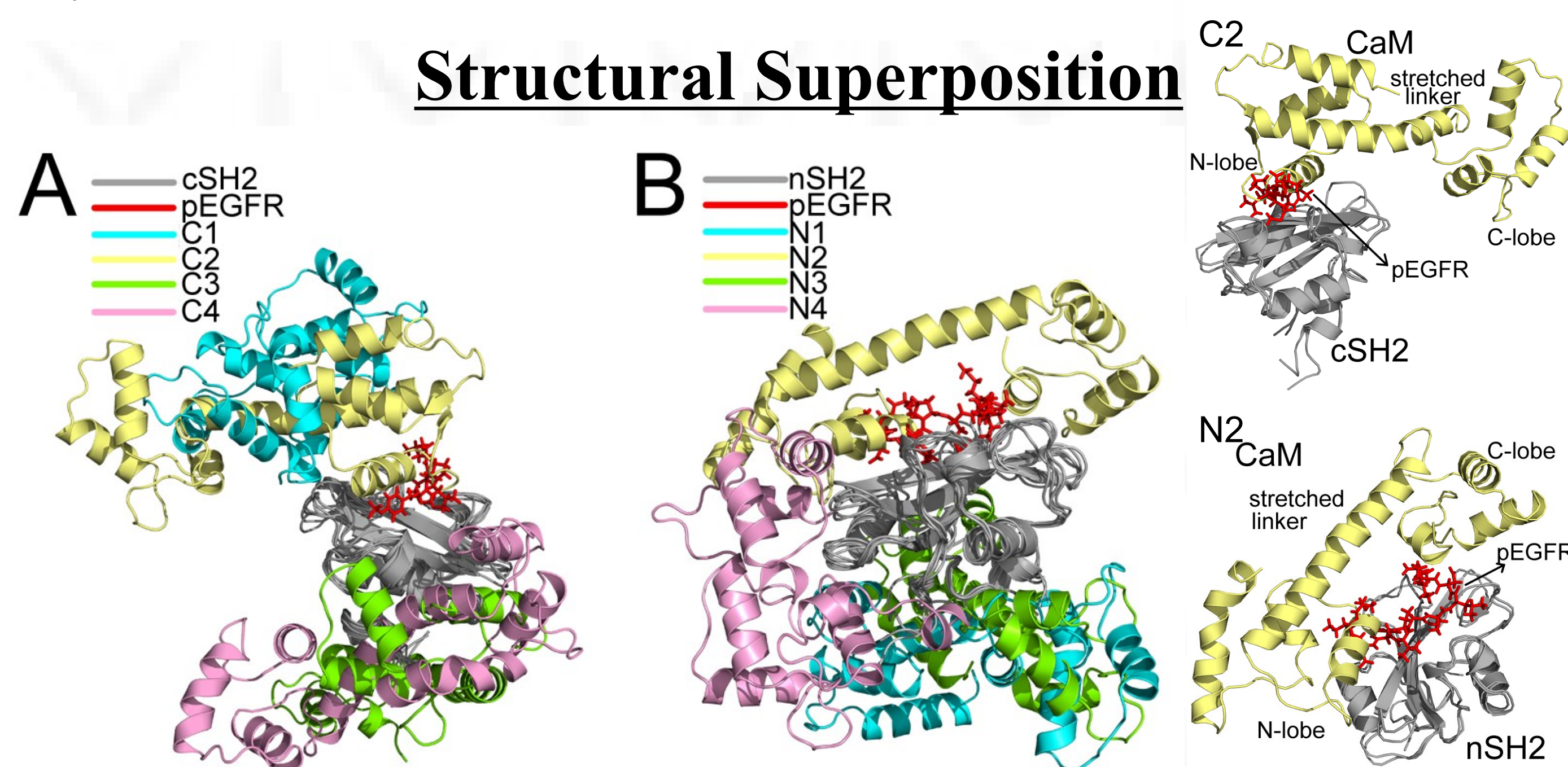
200 ns MD Simulations

Fig1. Structures for C1-C4 and N1-N4 after 200 ns MD simulations.

MM/GBSA Calculation

Systems	C1	C2	C3	C4	pEGFR-cSH2
ΔG (kcal/mol)	-17.43(11.54)	-30.56(10.19)	-39.83(10.46)	-15.84(7.87)	**-34.56(24.51)**
Systems	N1	N2	N3	N4	pEGFR-nSH2
ΔG (kcal/mol)	-31.35(10.49)	-56.62(10.88)	-63.23(12.84)	-95.68(11.78)	**-65.53(38.63)**

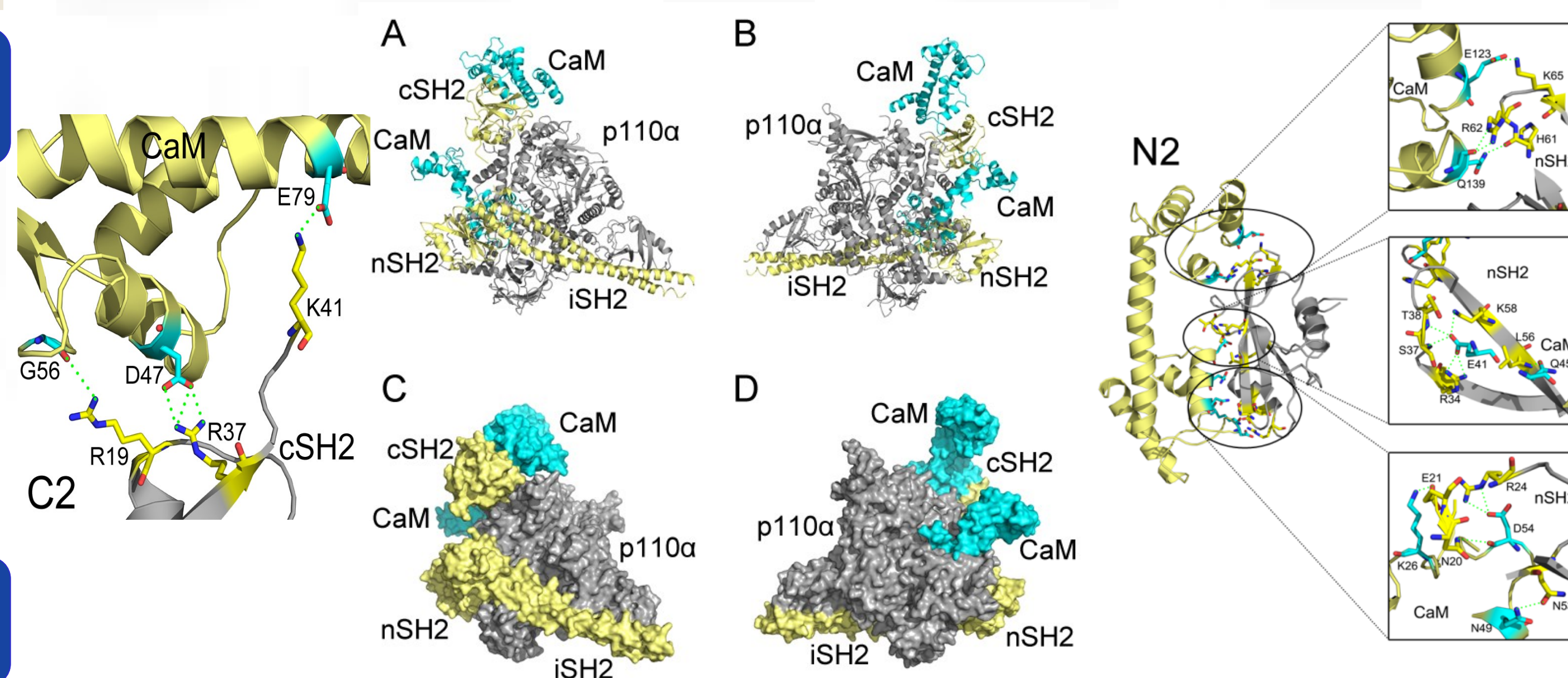➤ Binding free energy of C2/C3 and N2/N3/N4 are comparable to the ones of pEGFR-c/nSH2.

Structural Superposition

Fig2. Superposition of the 10 structures after 200 ns simulations.
➤ CaM has to mimic pEGFR so C2 and N2 are the ideal modes.

Interaction Details and Complex Model

Fig3. Complex models constructed based on C2/N2 and the detailed interaction mechanisms in C2/N2.

Significance and Prospects

- ✓ First reported CaM-PI3Kα complex structure.
- ✓ Revelation of the interaction modes and mechanisms.
- ✓ Theoretical support for the ternary complex hypothesis.
- ✓ Potential drug targets for cancer therapy.

Awards and Publications

Acknowledgements

References

Lu. *et al. Chem Rev.* 2016 Jun 8;116(11):6607-6665
Nussinov. *et al. Trends Cancer.* 2017 Mar;3(3):214-224

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