

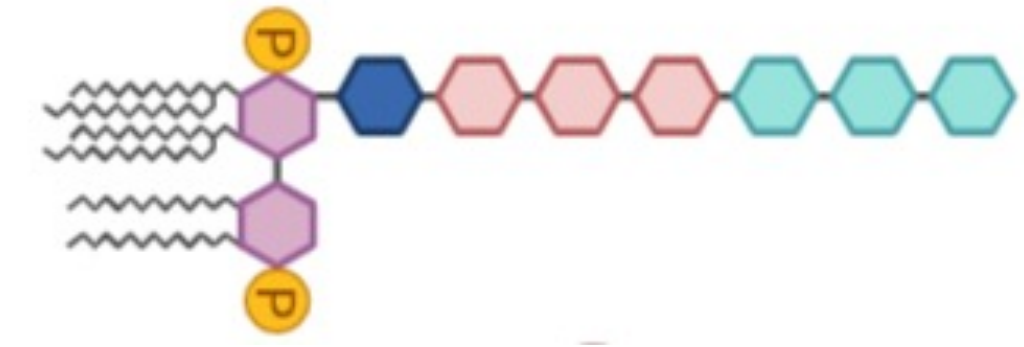


Determining How S100A9 Activates TLR4 Using Evolutionary and Biochemical Approach



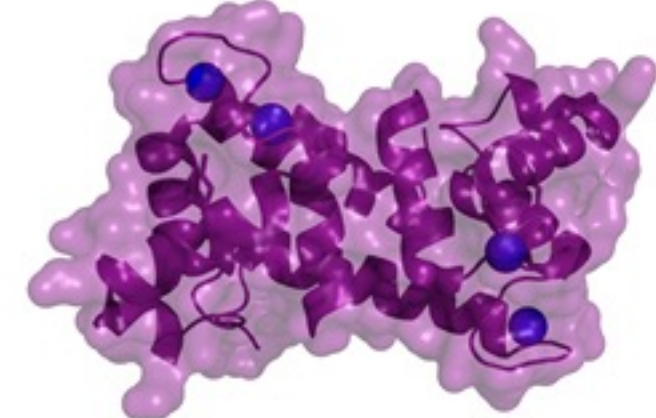
Jiayi Yin¹, Sophia Phillips^{1,2}, Mike Harms^{1,2} ¹University of Oregon, ²Department of Chemistry and Biochemistry

Introduction



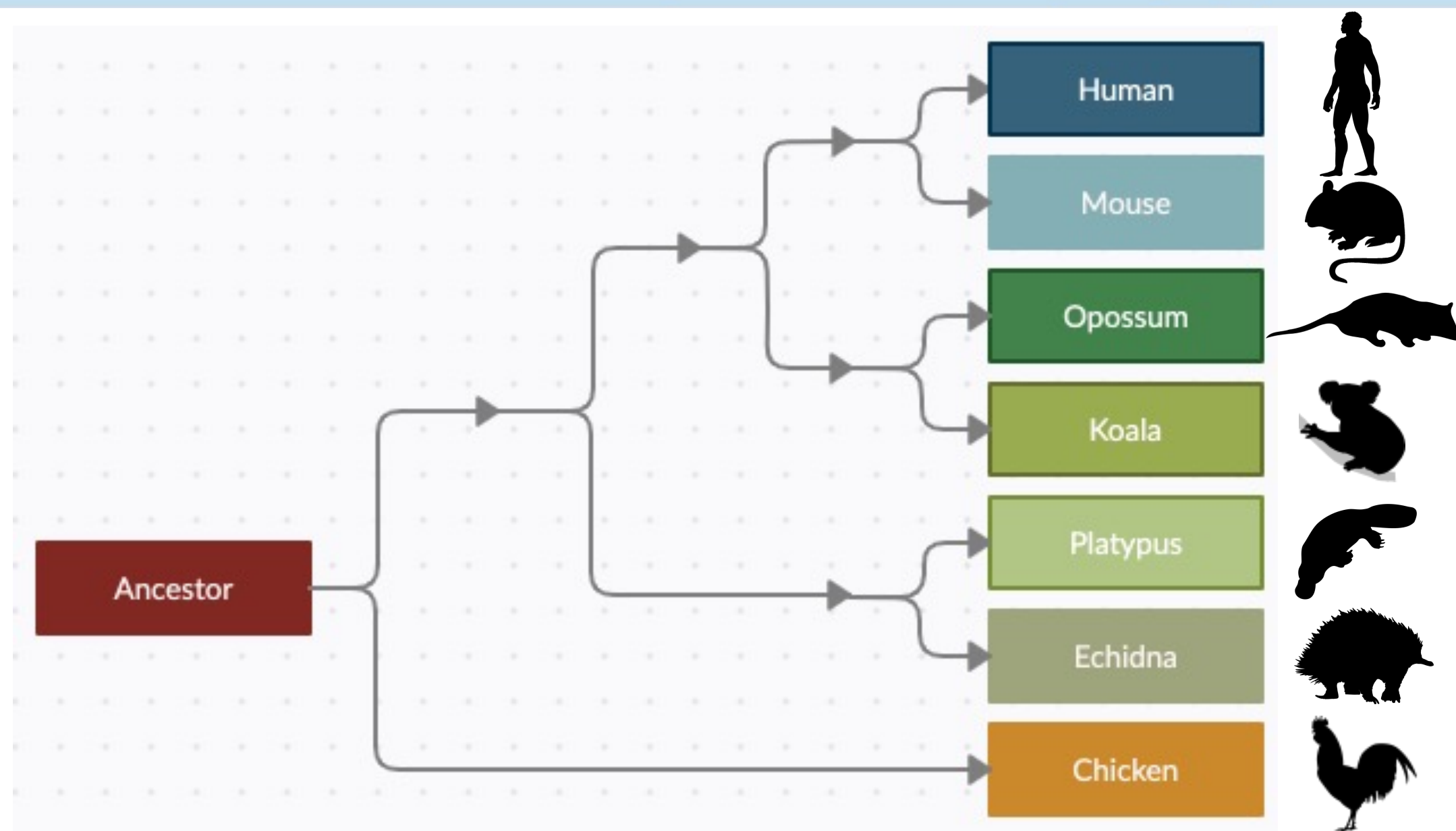
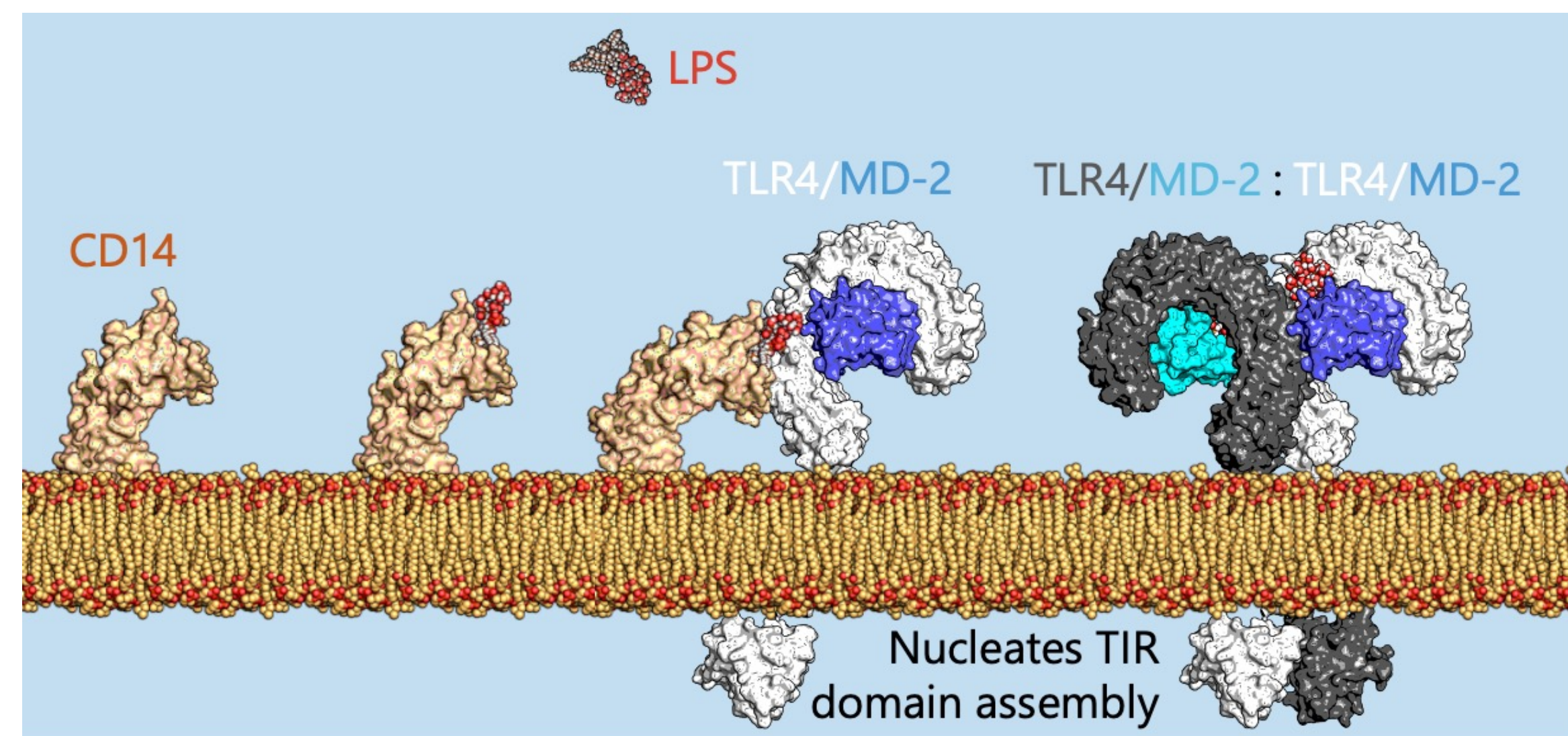
LPS

- Microbe Associated Molecular Pattern (MAMP)
- Hydrophobic small molecule
- Requires cofactors MD-2 & CD14
- Well defined interaction



S100A9

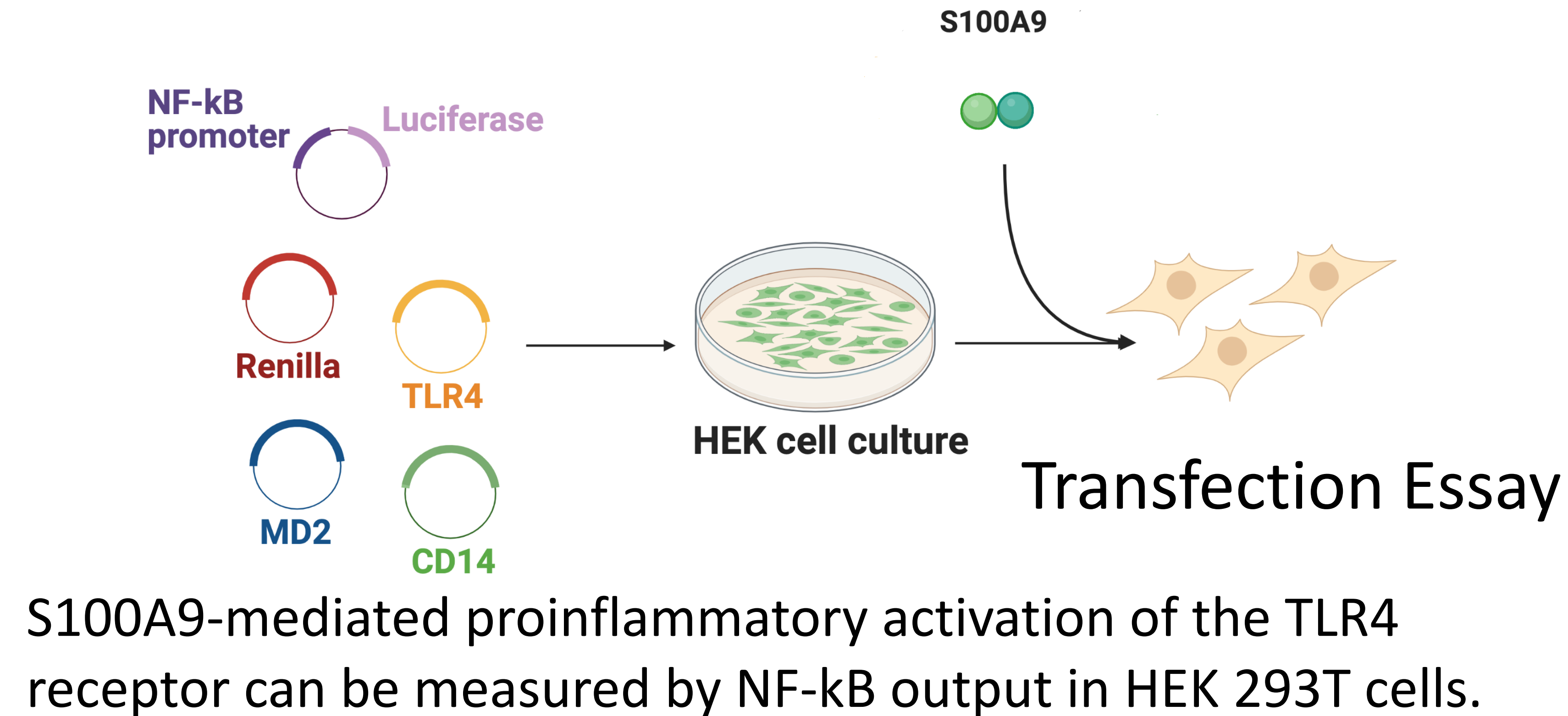
- Damage Associated Molecular Pattern (DAMP)
- Small soluble protein
- Requires cofactors MD-2 & CD14
- **Interaction unknown**



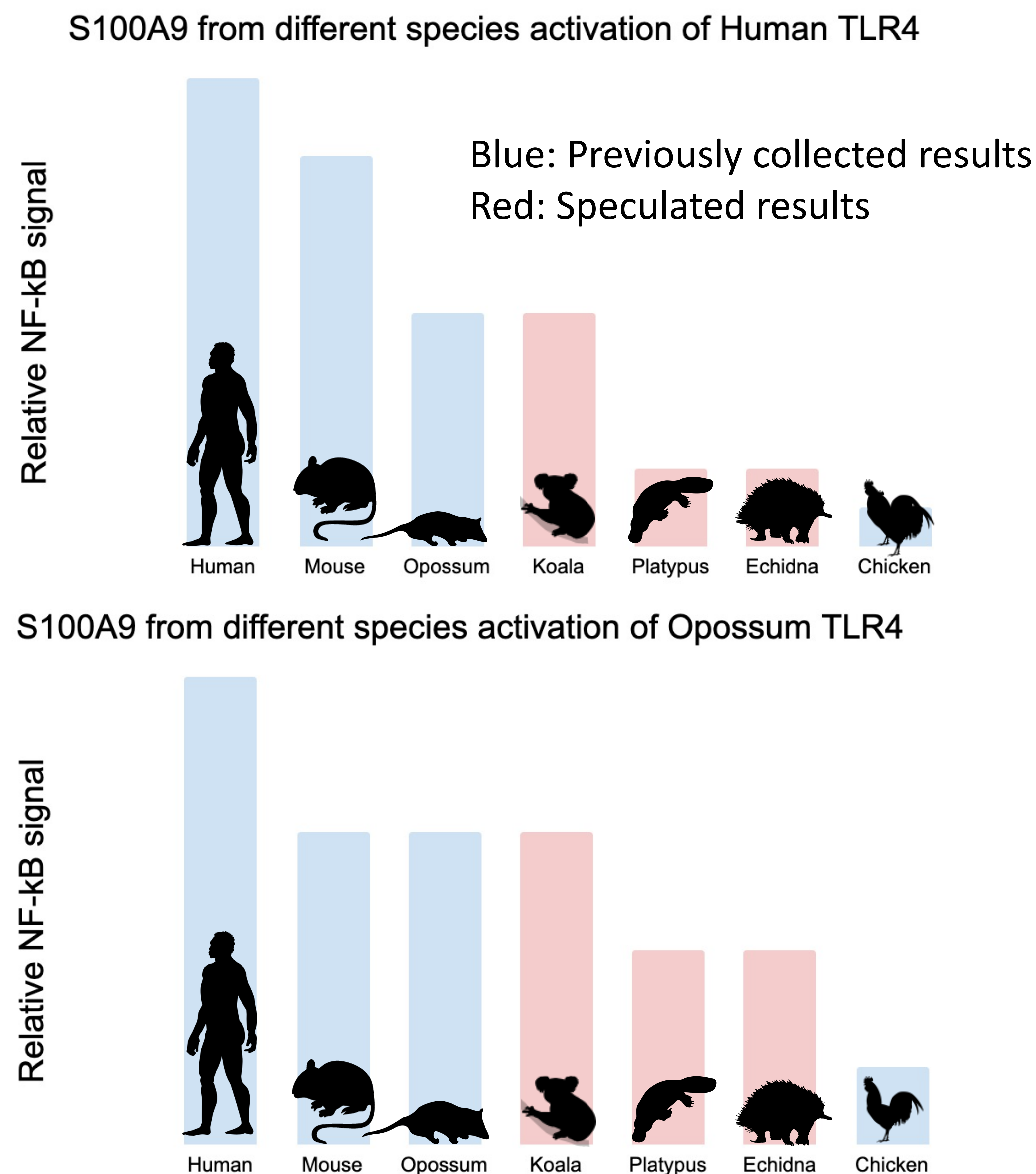
Research Question

How and when did S100A9 evolve a proinflammatory response with TLR4?

Methods



Expected Result



Possible Interpretations

- If data appear to match expectation: The data supports the hypothesis that S100A9 evolved to more strongly activate TLR4 in the ancestor of marsupial mammals.
- If data does not match expectation: It shows that the hypothesis is not correct and S100A9 evolution does not follow the evolutionary tree of life (species).

Future Direction

- Characterize Koala, Platypus and Echidna S100A9 activity.
- Reconstruct phylogenetic tree for S100A9 incorporating new modern day species
- Using site-directed mutagenesis, characterize how these mutations alter activity to identify important functionally related amino acids of S100A9

References

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Harman, J. L., Loes, A. N., Warren, G. D., Heaphy, M. C., Lampi, K. J., & Harms, M. J. (2020). Evolution of multifunctionality through a pleiotropic substitution in the innate immune protein S100A9. *eLife*, 9, e54100.

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Acknowledgments

Thank you to the lovely Harms Lab!