

Molecular Basis of Selectivity & Activity for the Antimicrobial Peptide Lubelisin

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What is an antimicrobial peptide? (AMPs)

Small peptides, typically composed of 12–50 amino acids, which possess broad-spectrum activity against bacteria, viruses, fungi, and even a subset of cancer cell types.¹

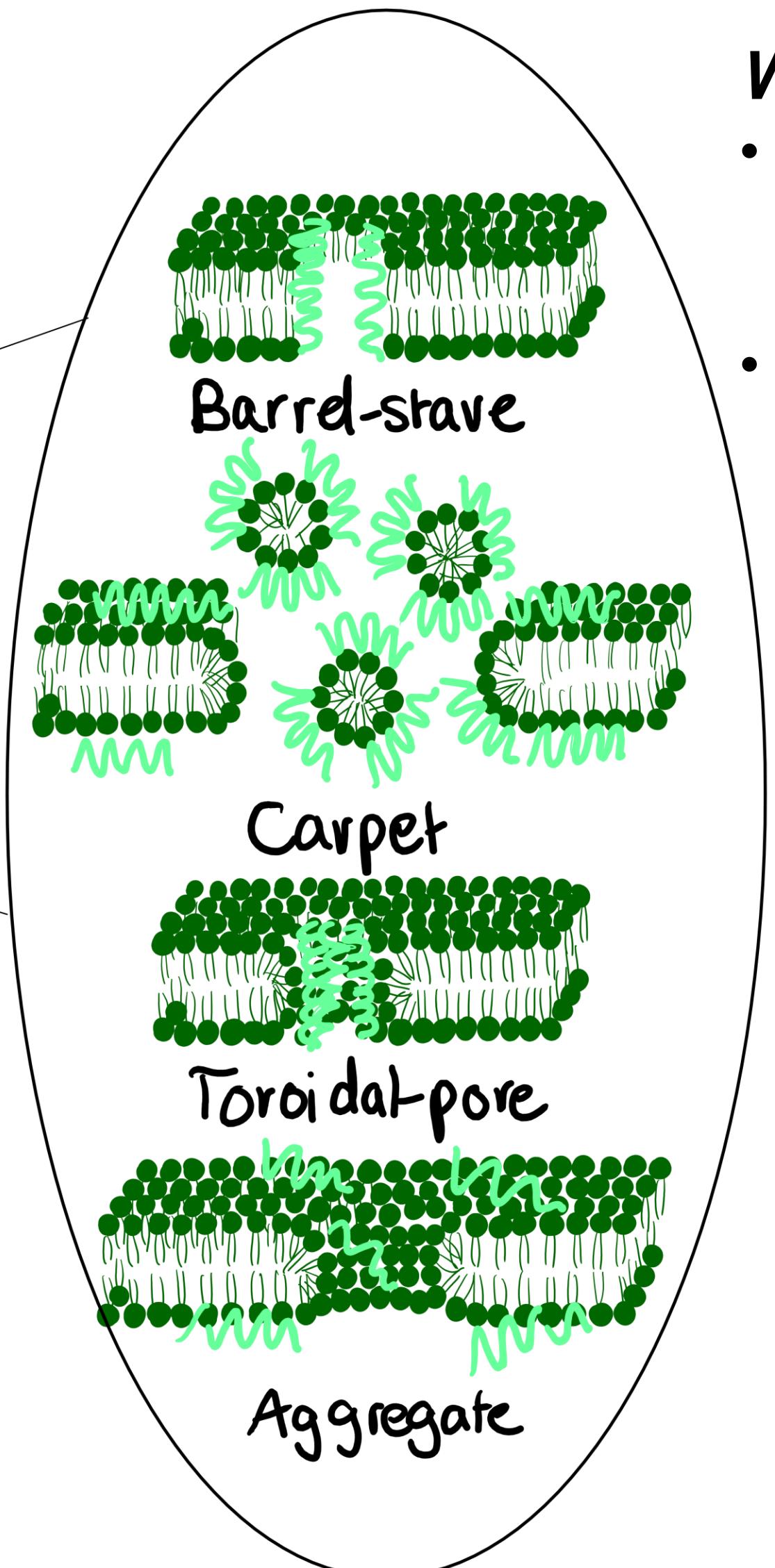
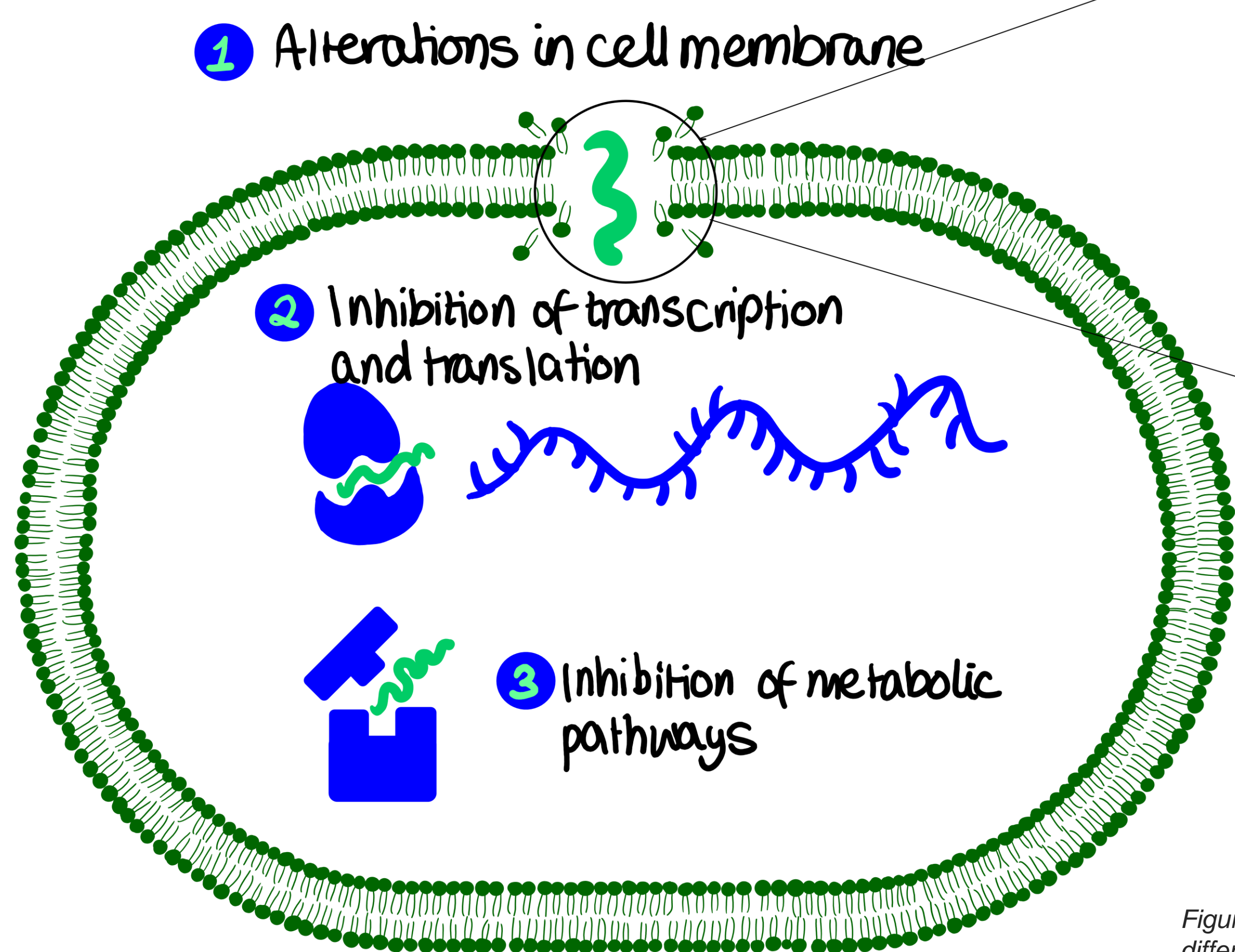


Figure 1: Different actions of AMPs on bacterial cells and the different models of membrane disruption.^{3,4}

Why we need AMPs

- Microbial antibiotic resistance is a major threat to human health; discovery of new therapeutics able to attack these microbes is therefore vital.
- The mechanism of action employed by AMPs is less likely to induce microbial resistance, offering a novel alternative to traditional antibiotics.¹

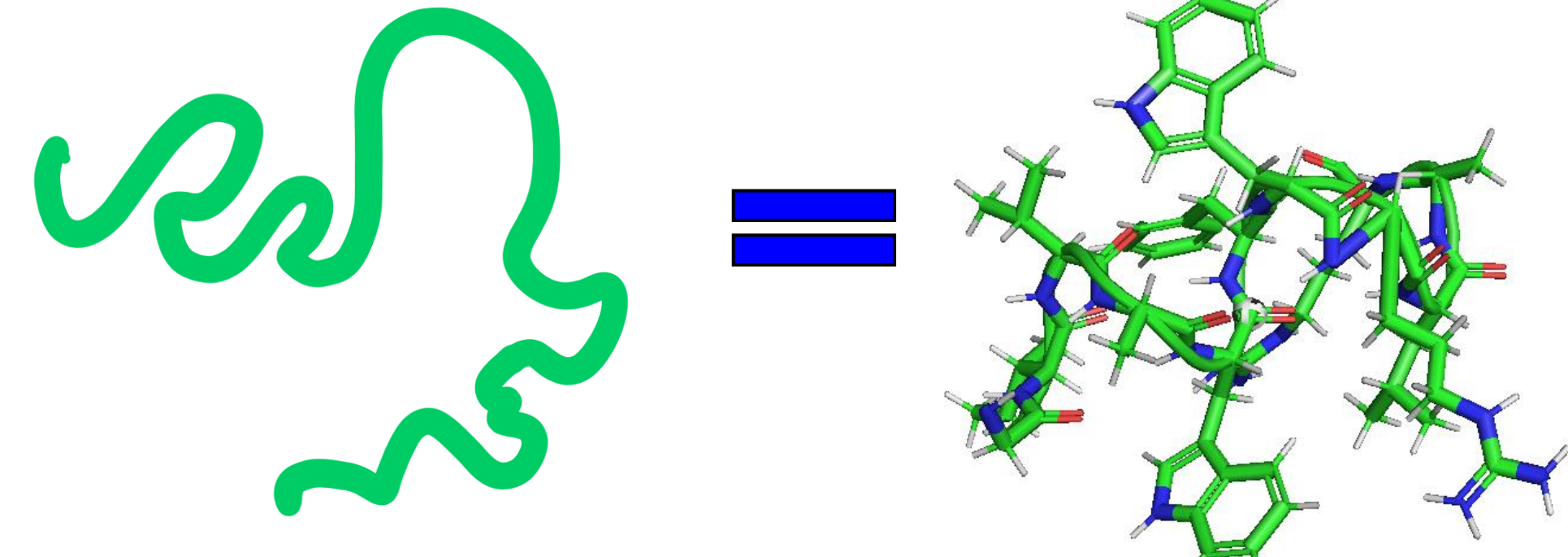


Figure 2: Lubelisin models: Hand-drawn cartoon approximation and Pymol generation

Our model: Lubelisin²

- 11 amino acid peptide with a net positive charge (+2)
- Can kill strains of methicillin-resistant *Staphylococcus aureus* (MRSA) USA300 and EMRSA-15 within 30 min
- Low cytotoxicity against both human and sheep erythrocytes, yielding a therapeutic index of 0.43
- Membrane permeabilisation assays suggest the AMP works by inducing cytoplasmic membrane damage

Key research question: What is the mechanism of action?

3-Step Methodology

Circular Dichroism

Peaks at 208 and 222nm

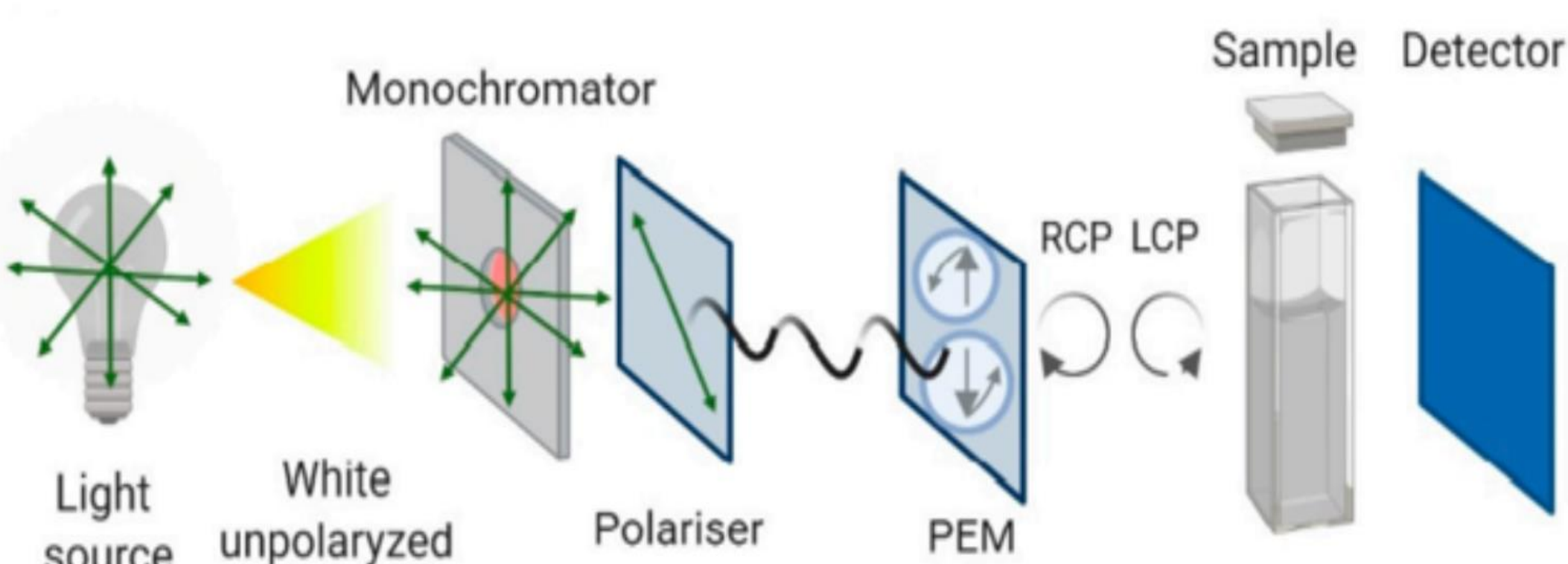


Figure 3: Schematic of a Circular Dichroism (CD) Spectropolarimeter. The CD machine measures differential absorption of left and right circularly polarized light to analyse the chiral properties of a sample.⁵

Fluorescence

Blue shift of Trp emission peak

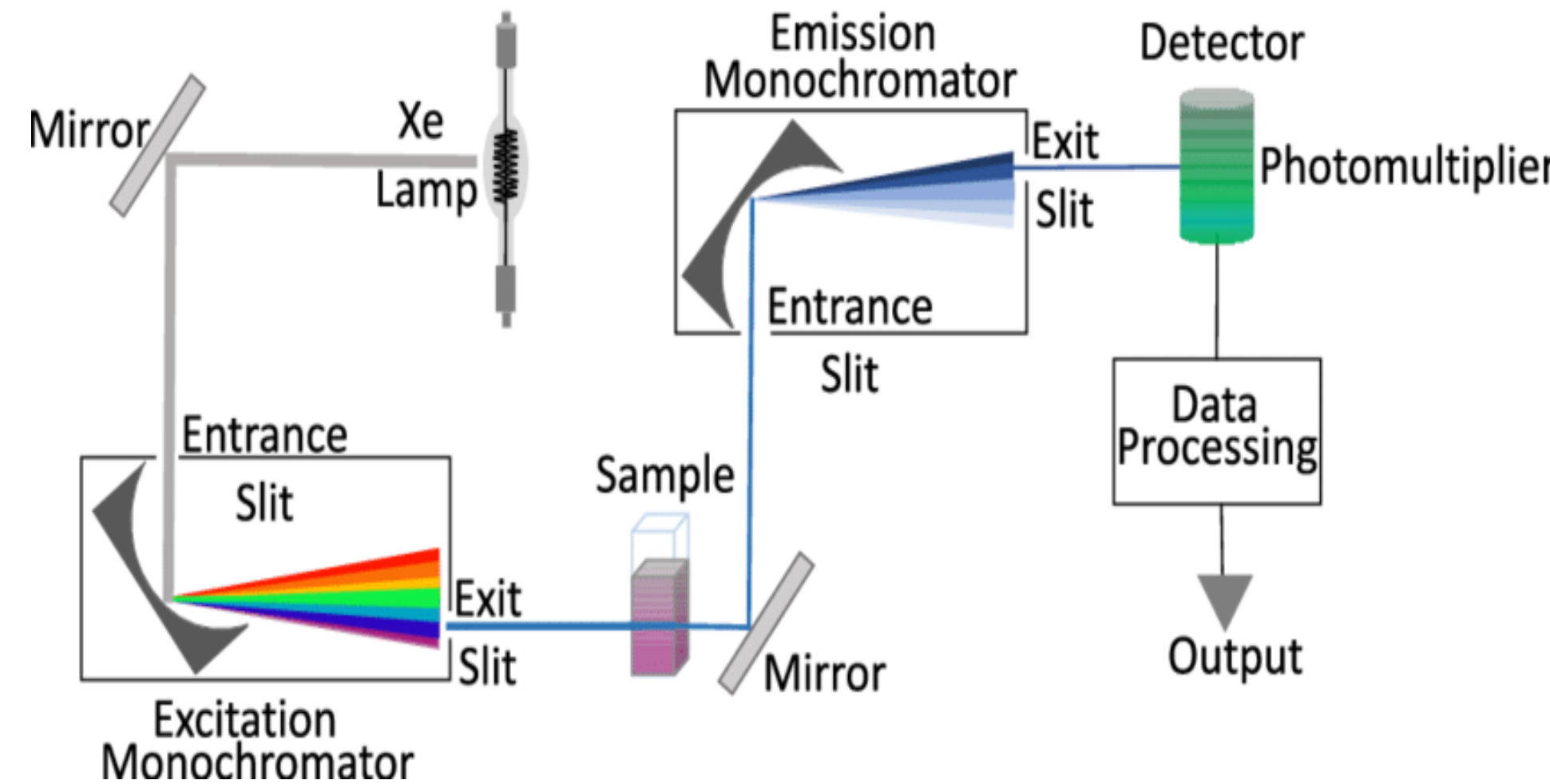


Figure 4: Schematic of a Fluorimeter. The fluorimeter measures fluorescence intensity emitted by a sample after excitation by a specific wavelength of light.⁶

NMR

Sequential chemical shift assignments

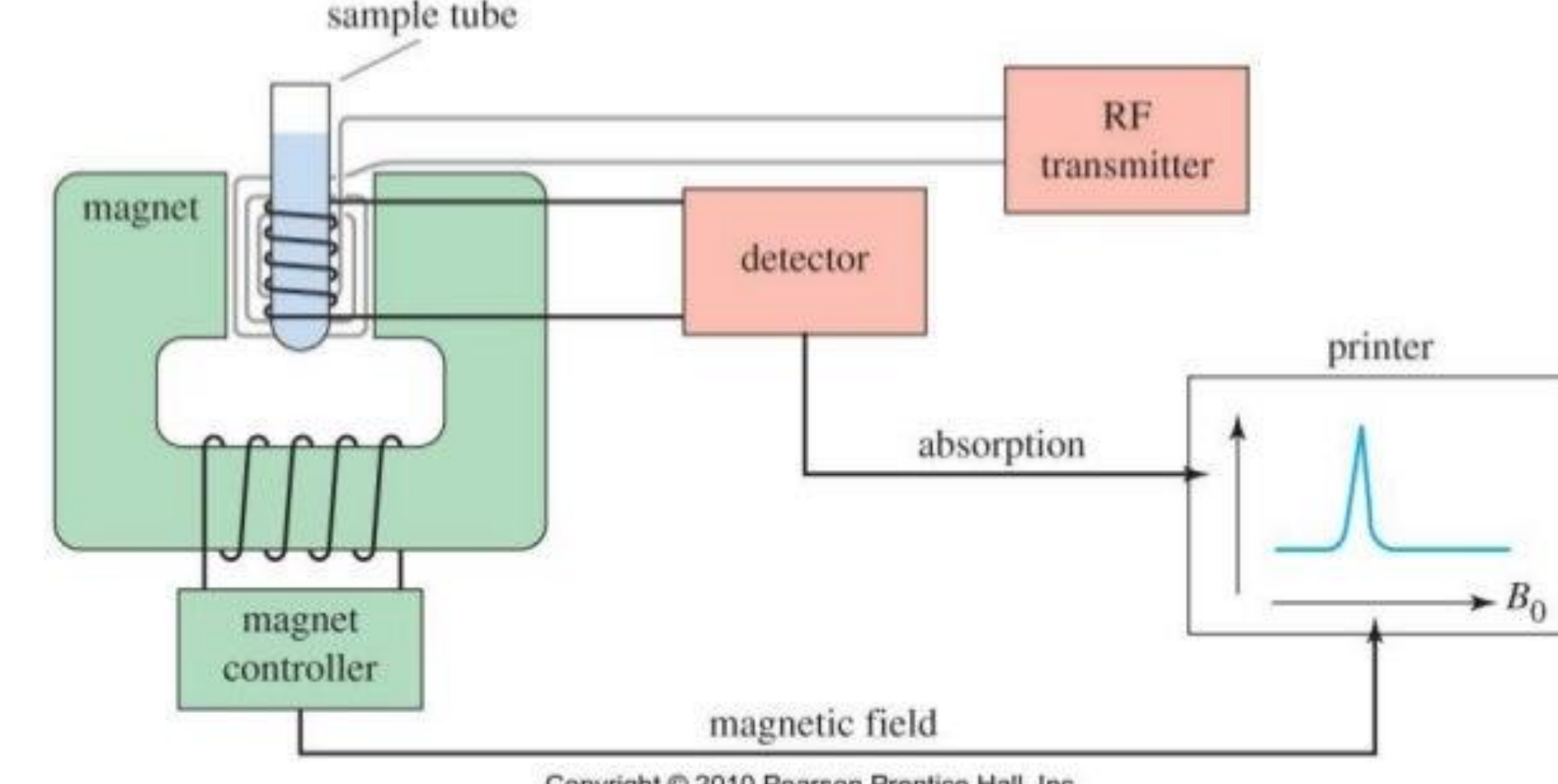
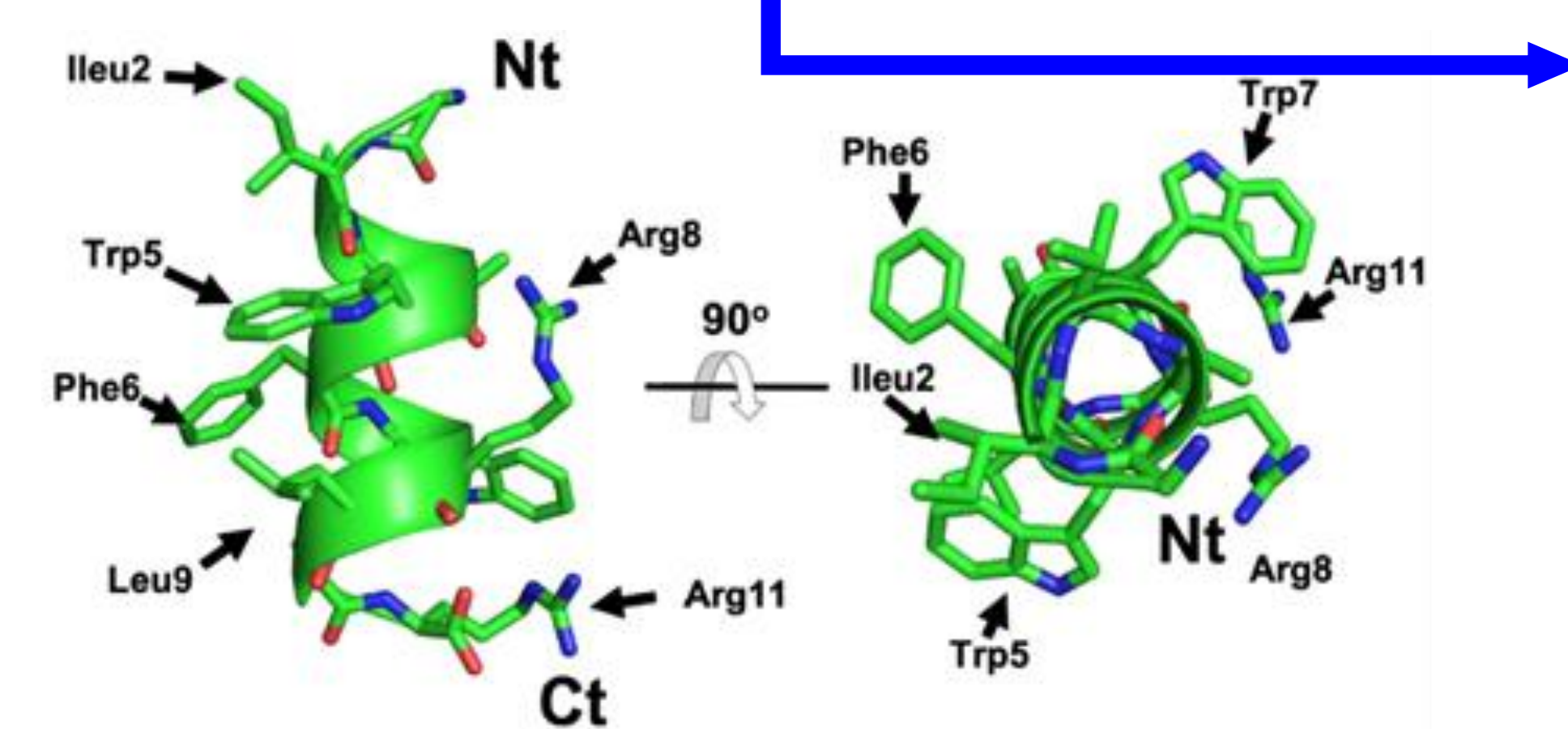
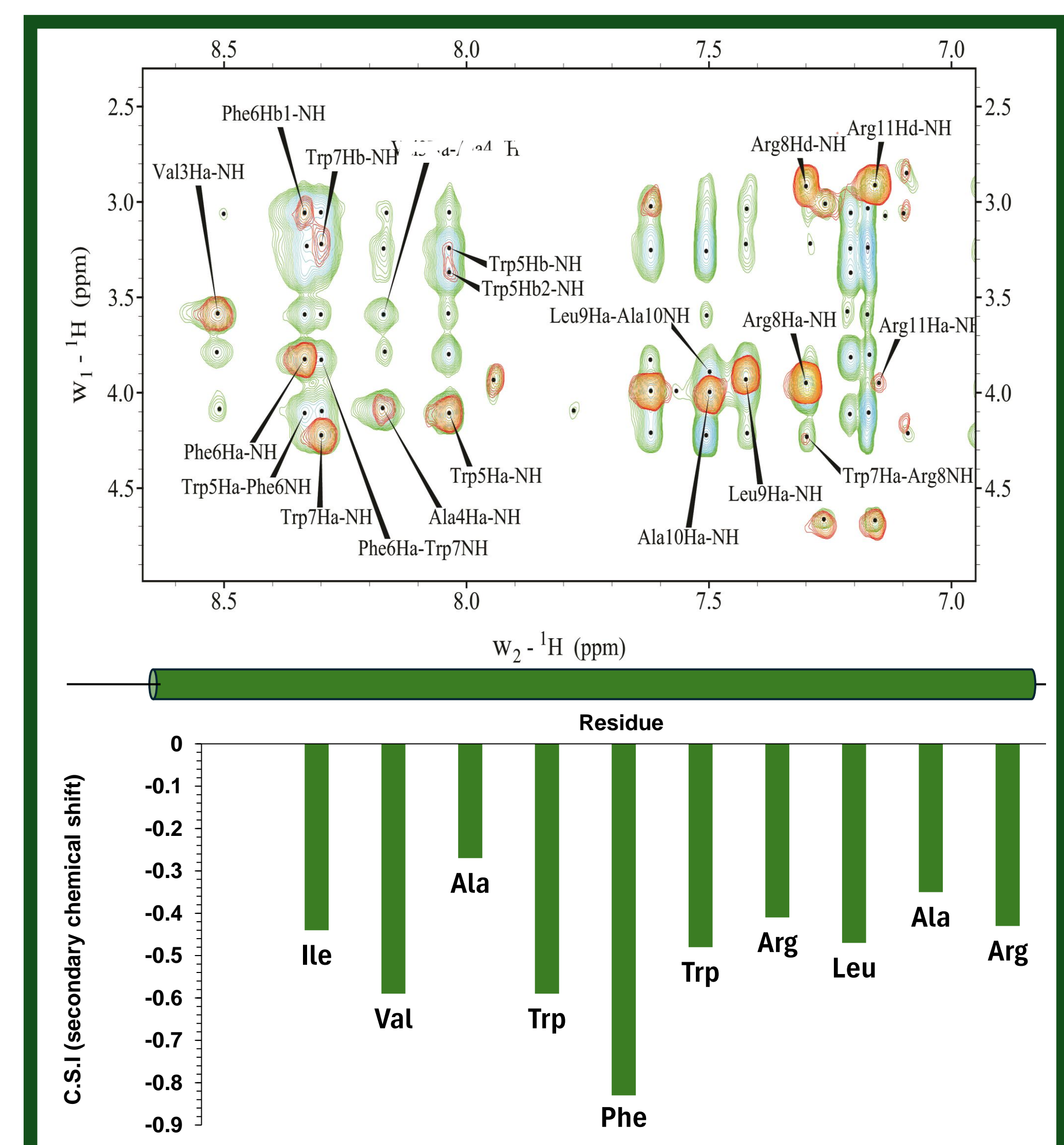
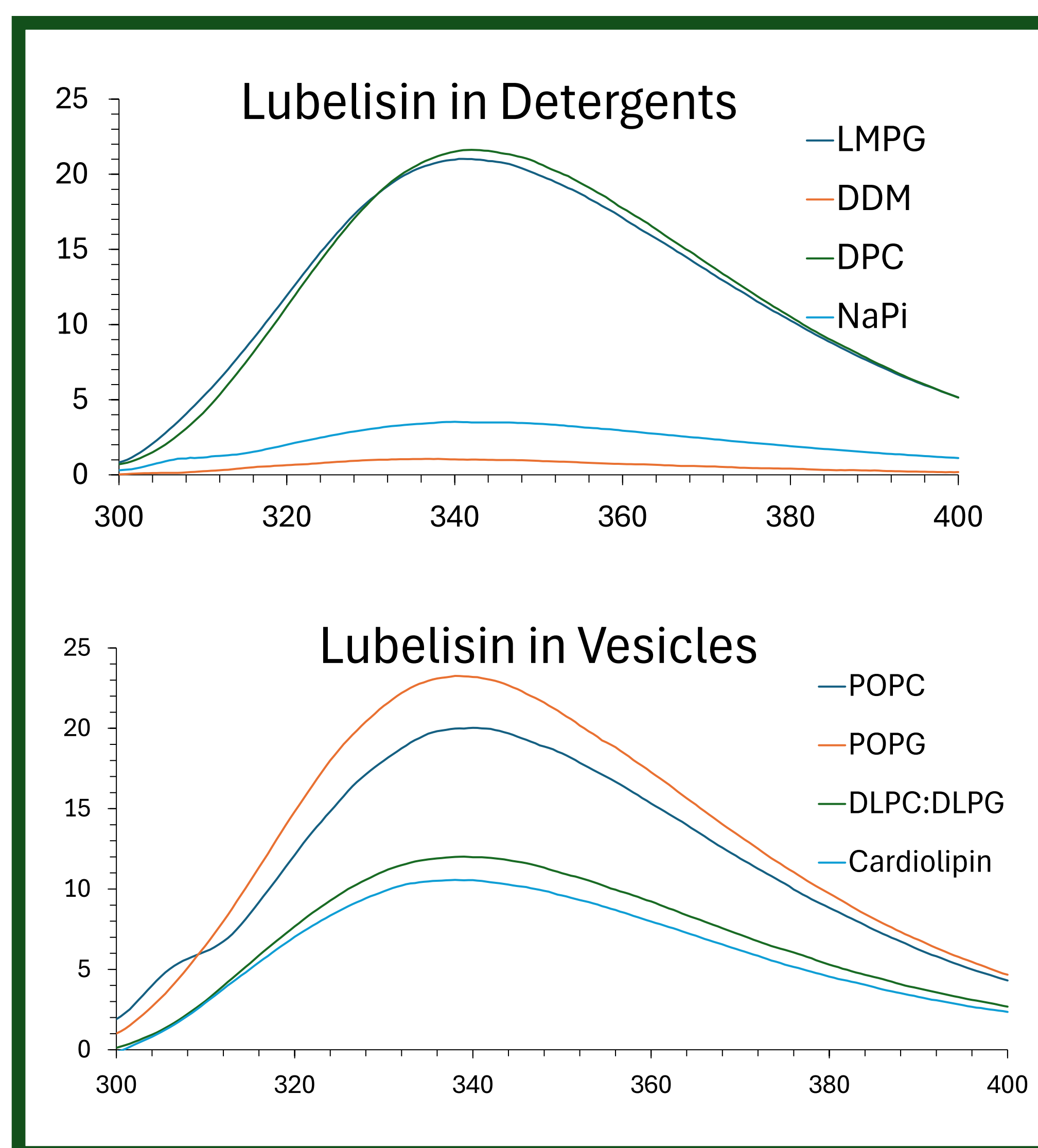
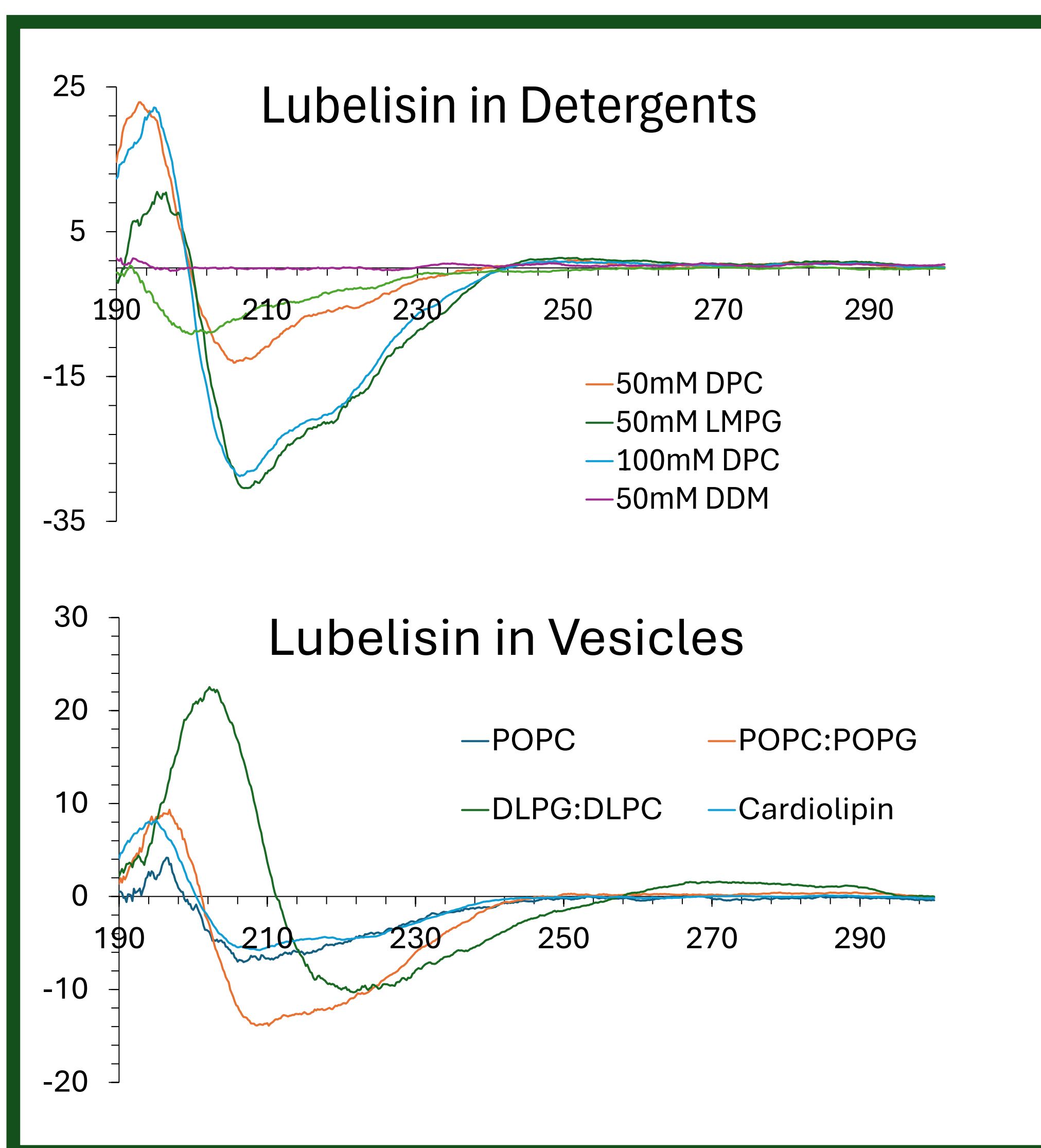


Figure 5: Schematic of an NMR Spectrometer. The NMR spectrometer detects nuclear spin transitions in a magnetic field, providing structural and dynamic information about molecules.⁷

Results:



Conclusion:

Lubelisin forms a helical secondary structure in DPC, LMPG and POPC:POPG which suggests the mechanism of action is alterations in the cell membrane.

References:

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