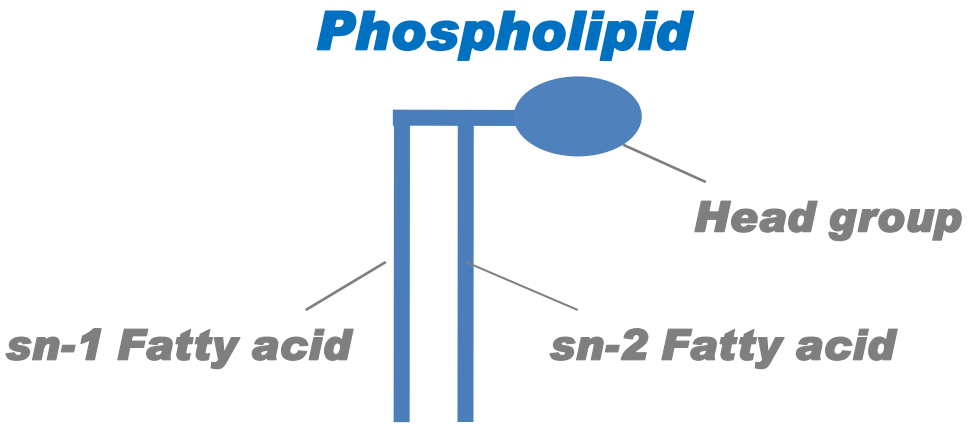
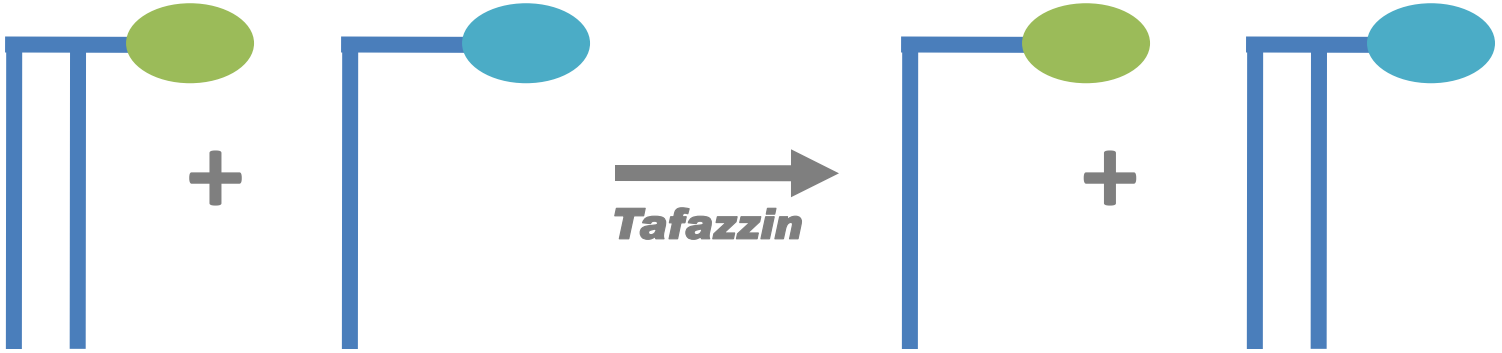
The Mechanism of Acyl-Specific Phospholipid Remodeling by Tafazzin

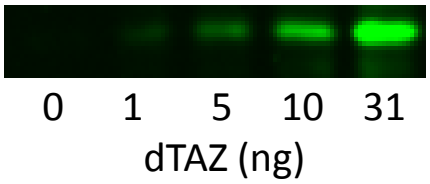
Michael Schlame

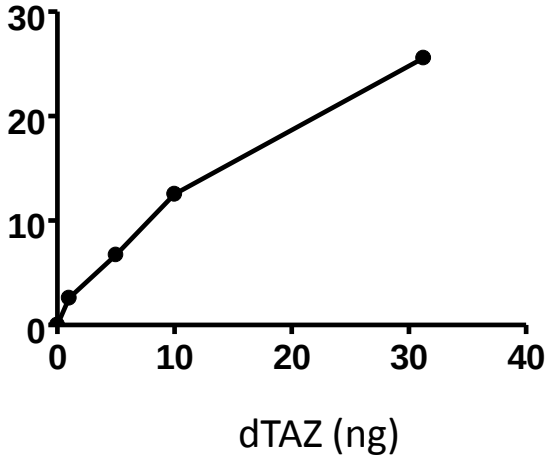

Phospholipid
Head group
sn-1 Fatty acid
sn-2 Fatty acid


Tafazzin

Tafazzin Reacts with < 1% of Mitochondrial Lipids

Mitochondria	dTAZ pmol/mg	PL nmol/mg	PL/dTAZ
Fly WT	1.1±0.1	0.82±0.23	745
Sf9 expressing dTAZ	20±3	1.69±0.31	85
Sf9 expressing dTAZ (high level)	86±2	4.38±1.02	51





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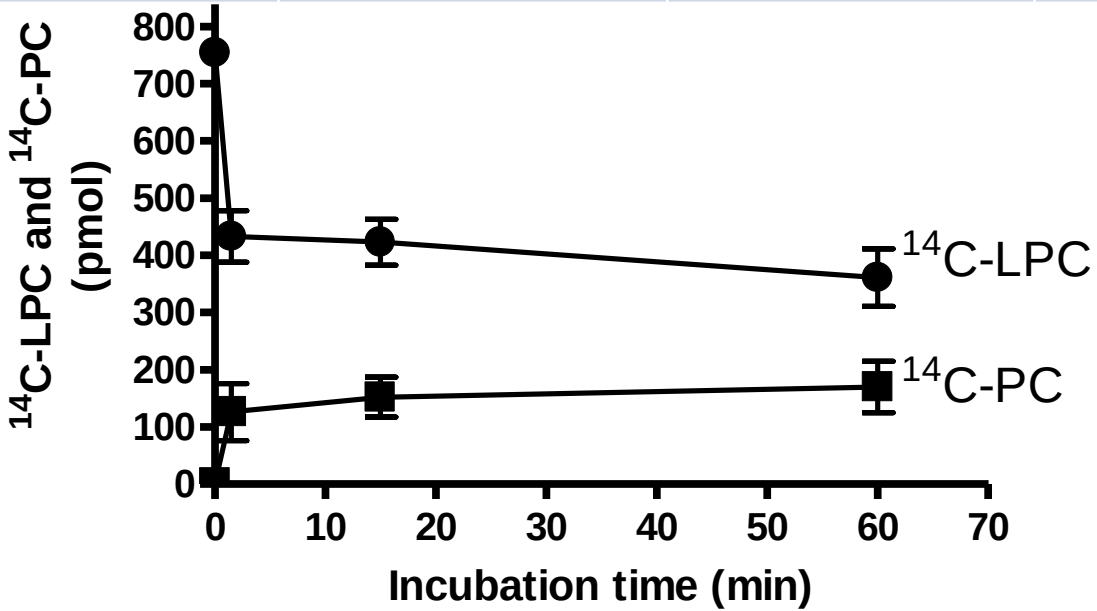
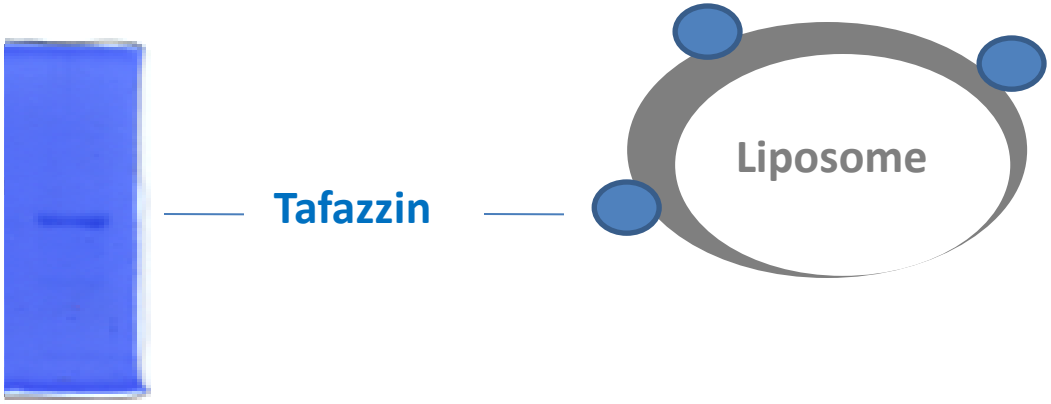


Tafazzin + PC/LPC Liposomes



Tafazzin + PC/LPC Liposomes

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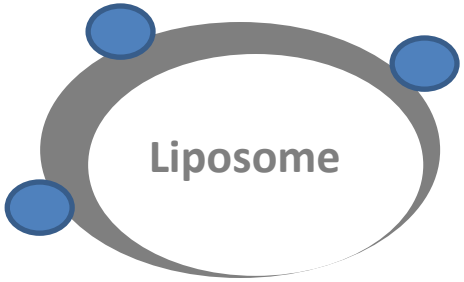
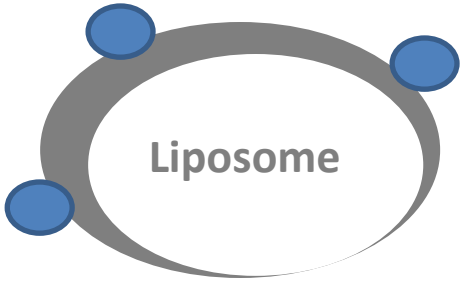


1-palmitoyl-2-linoleoyl-PC + 1-[^{14}C]palmitoyl-2-lyso-PC ⇔ 1-[^{14}C]palmitoyl-2-linoleoyl-PC + 1-palmitoyl-2-lyso-PC

1-palmitoyl-2-linoleoyl-PC	1-palmitoyl 2-lyso PC	Ratio
20 nmol	1 nmol	20:1
1,000 cpm	45,000 cpm	1:45

Tafazzin + PC/LPC Liposomes

Tafazzin



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1-palmitoyl-2-linoleoyl-PC	1-palmitoyl 2-lyso PC	Ratio
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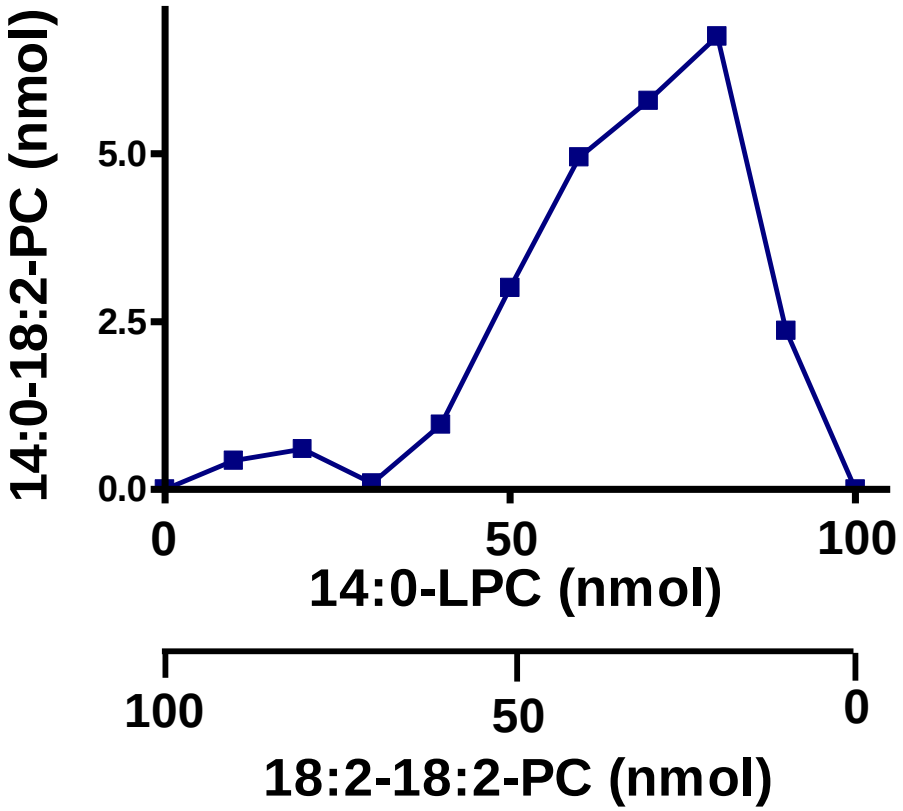
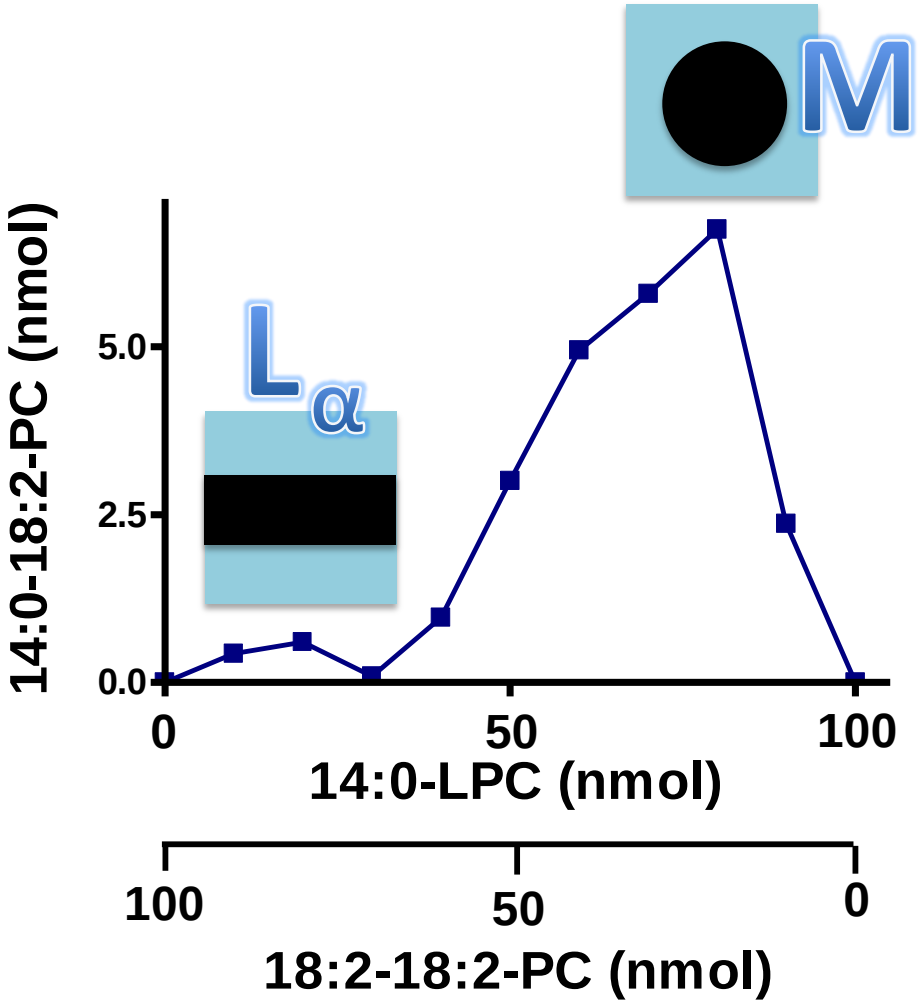
Supernatant: 82% [^{14}C]PC

Liposomes: 100% PC

Tafazzin + PC/LPC Liposomes

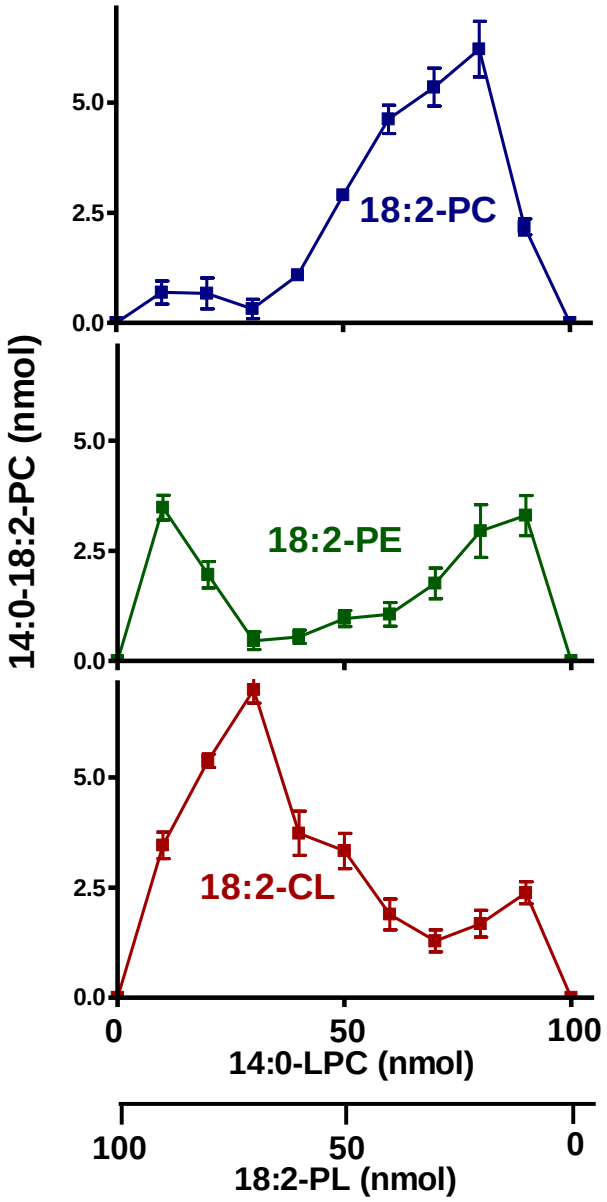


Tafazzin + PC/LPC Liposomes



^{31}P NMR

Tafazzin Reacts only with Non-Bilayer Lipids



Phosphatidylethanolamine

Cardiolipin

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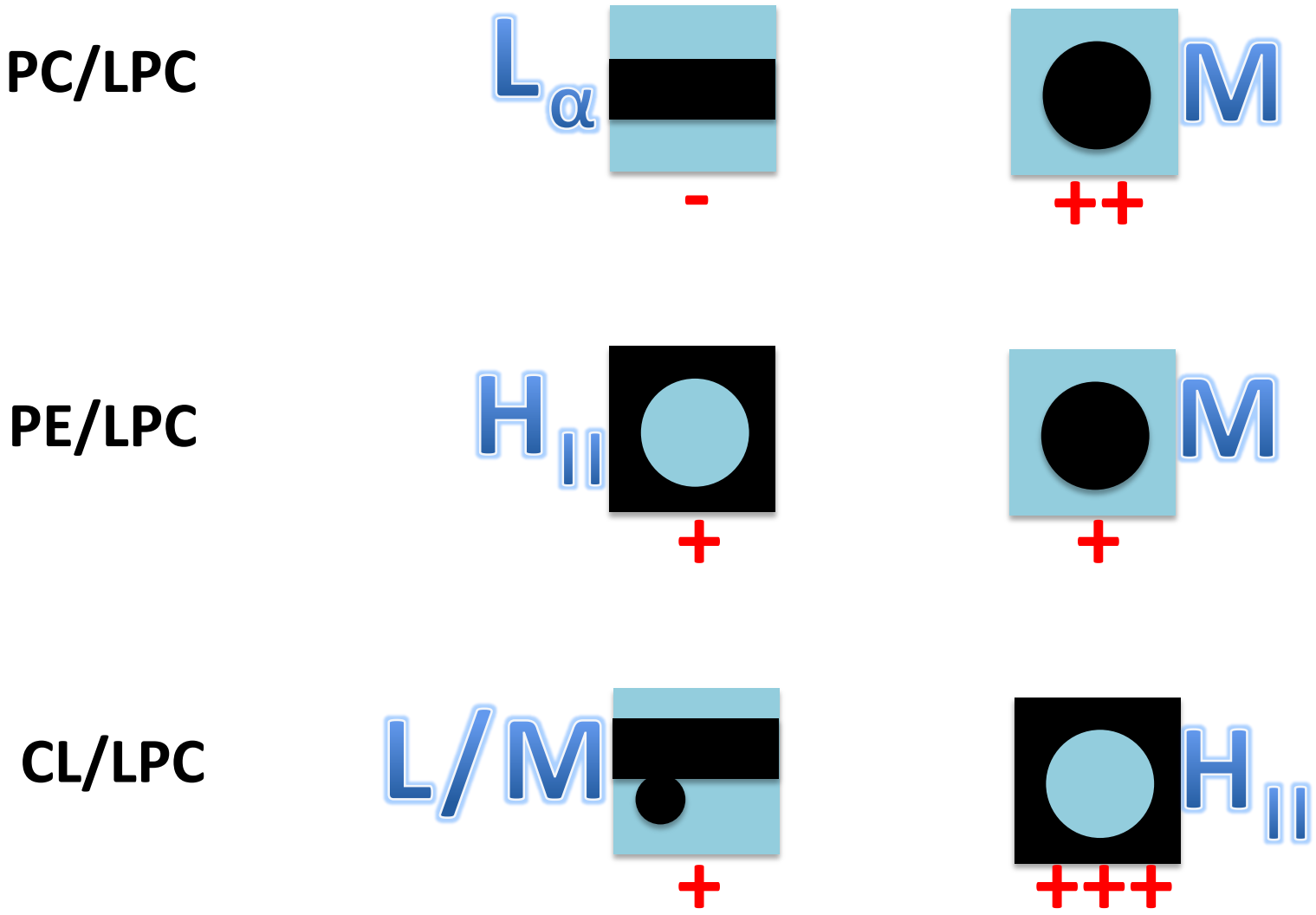
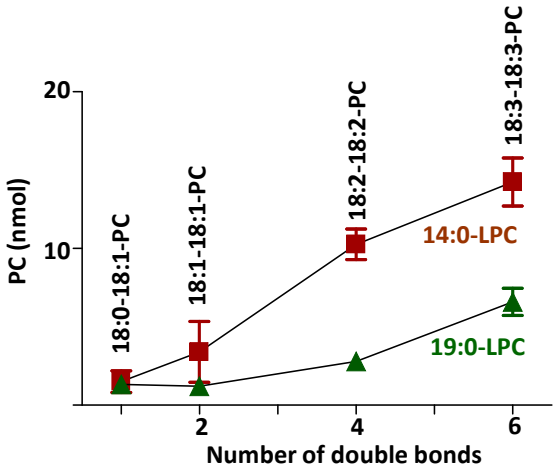
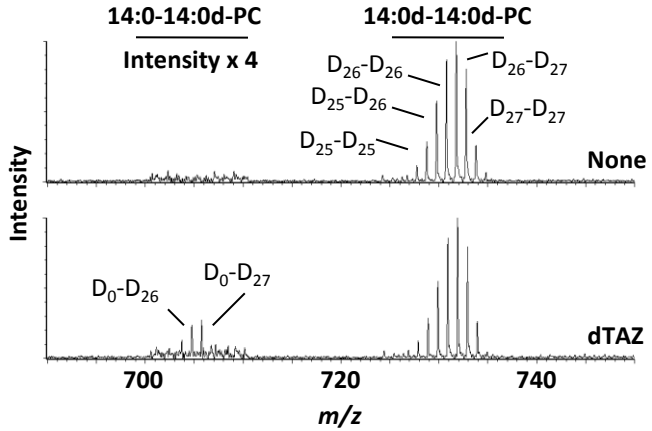


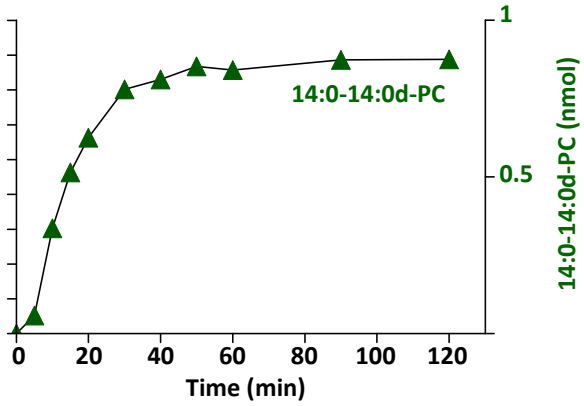
PC/LPC Micelles:
Transacylation Activity
Increases with the Number of Double Bonds and Decreases with the Chain Length



Tafazzin Transfers 14:0 Acyl Groups but does Not Achieve Complete 14:0 Exchange between PC & LPC

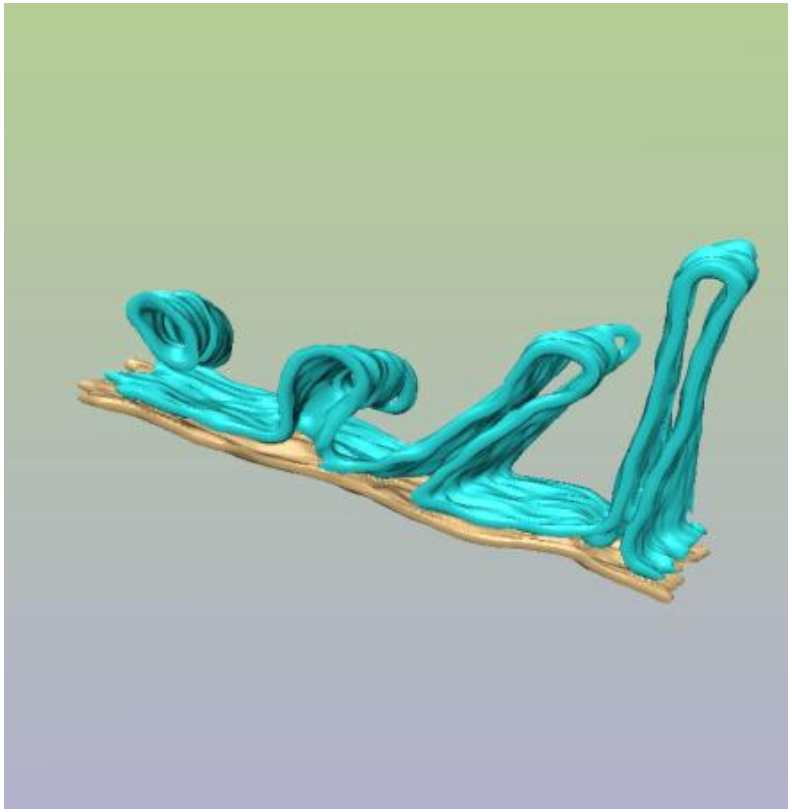
14:0-LPC + 14:0d-14:0d-PC → 14:0-14:0d-PC + 14:0d-LPC

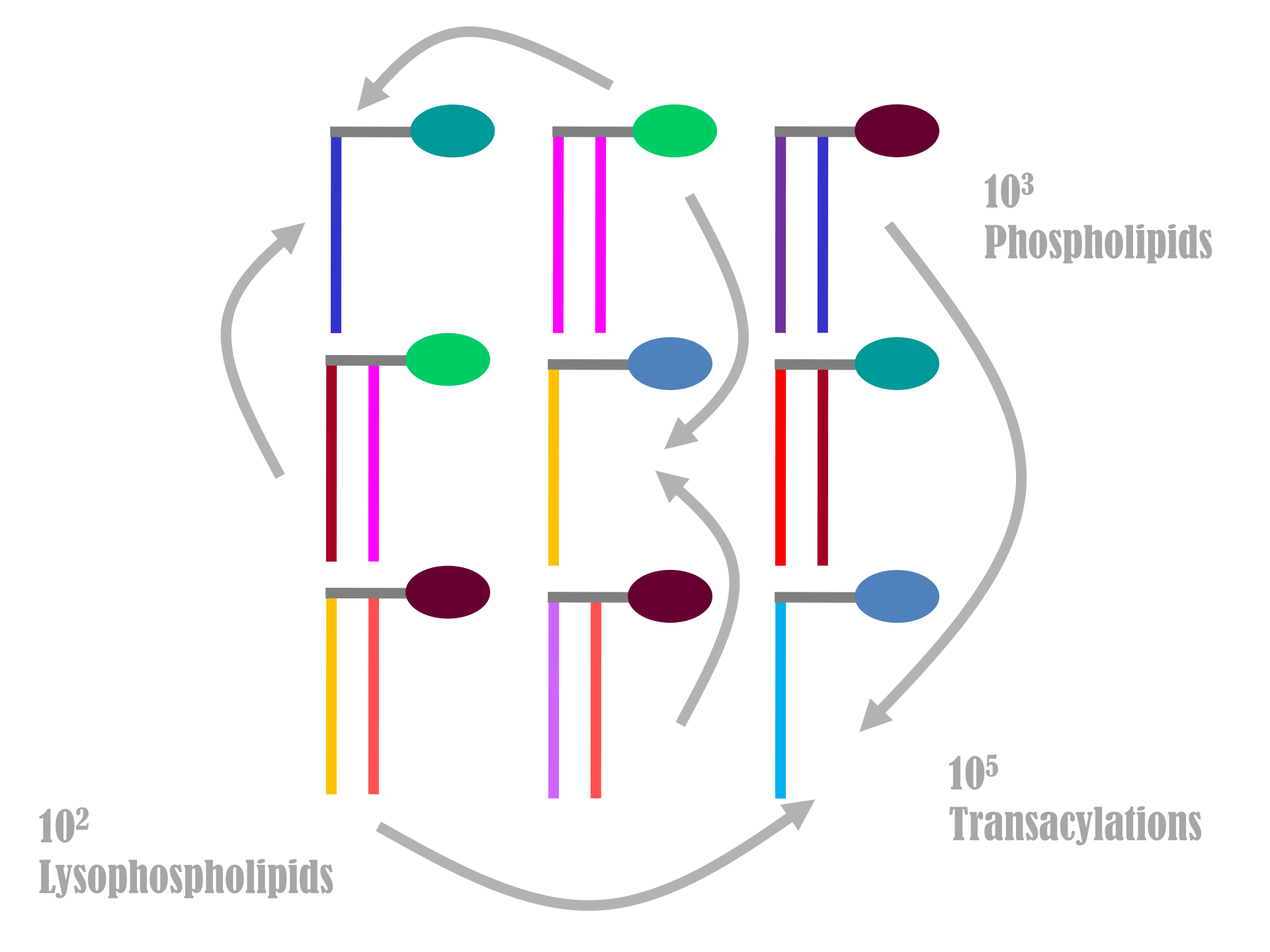




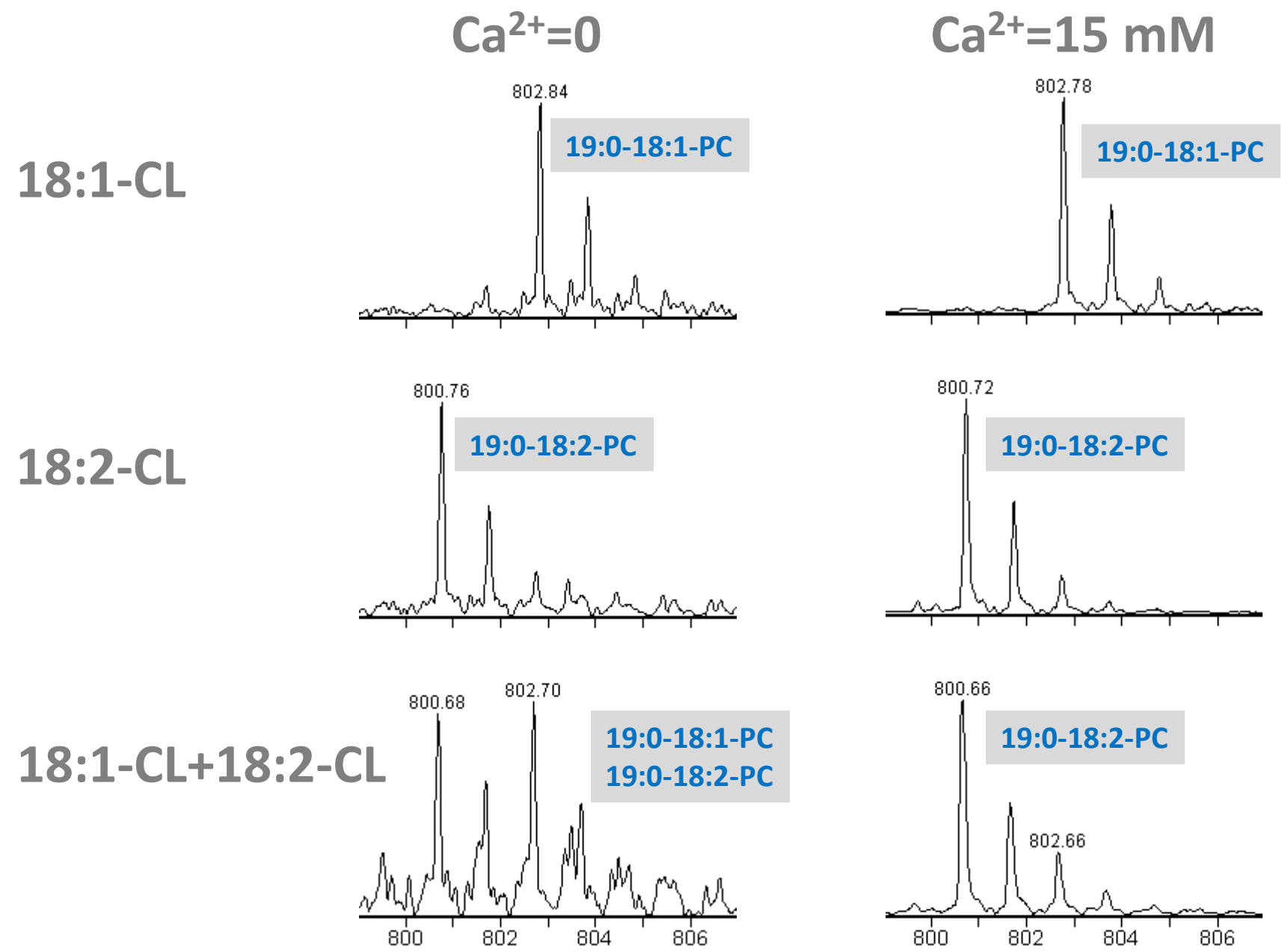
Conclusions I

- Tafazzin does not react with lipids in the bilayer state.
- Instead, it requires substrates to form assemblies with high positive or negative curvature, such as micelles or inverted hexagonal structures.
- Low lipid packing order promotes transacylation, presumably because it facilitates ideal mixing of PLs and LPLs.

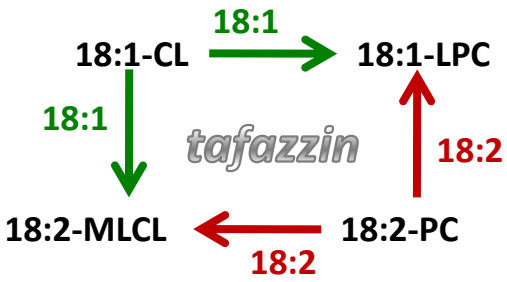



10^3
Phospholipids
10^5
Transacylations
10^2
Lysophospholipids

Transition into H_{II} Phase Induces Acyl Specificity



Reconstitution of Mitochondrial Phospholipid Remodeling In Vitro



CL	:	MLCL	:	LPC	:	PC
40	:	10	:	10	:	40

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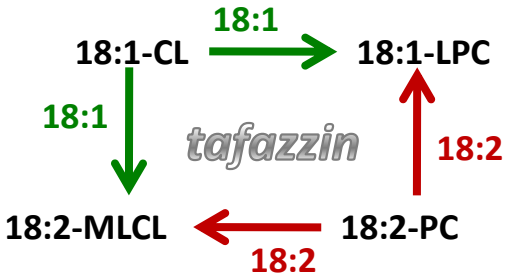

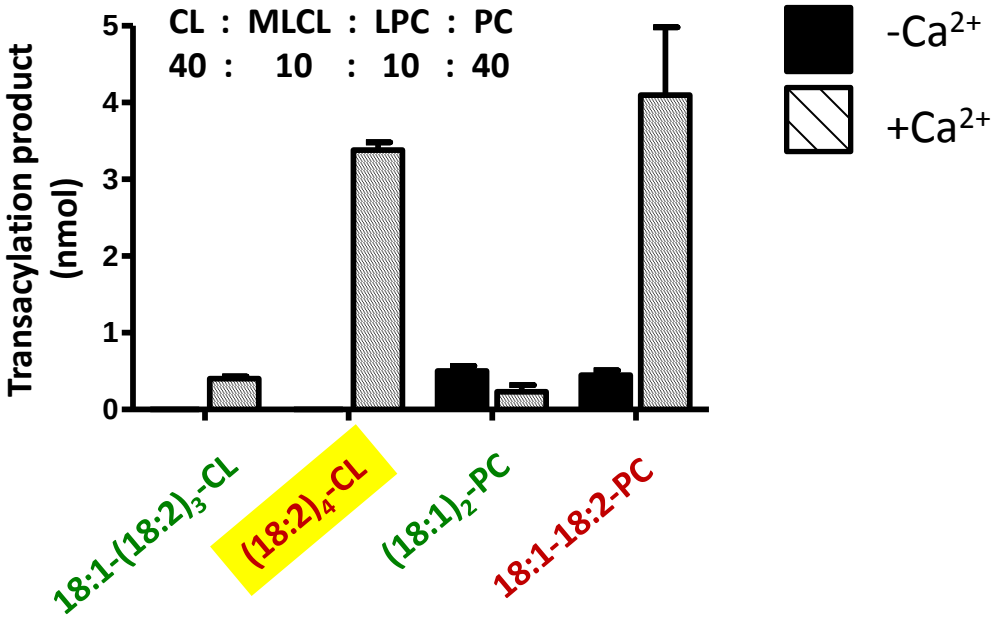

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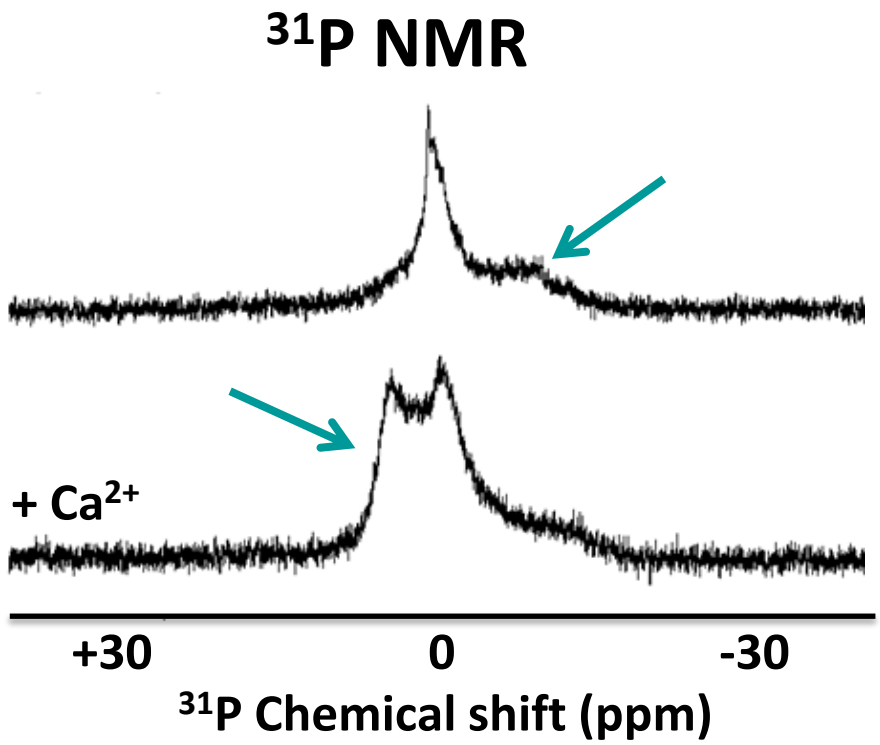
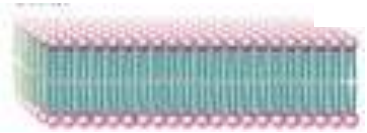
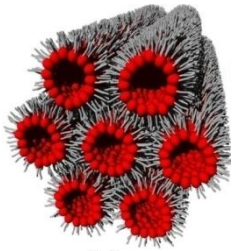




L_α



H_{II}

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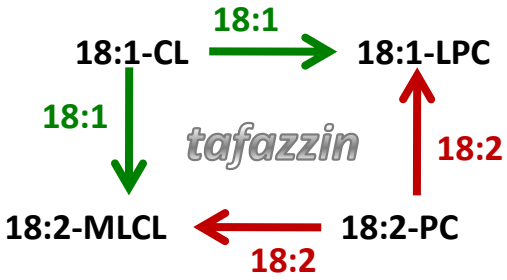
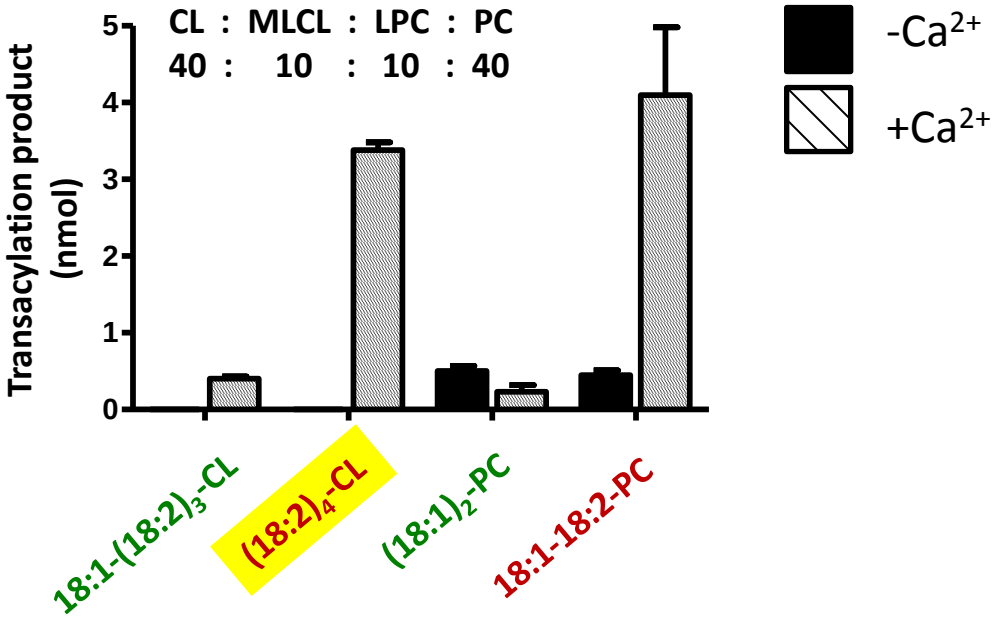
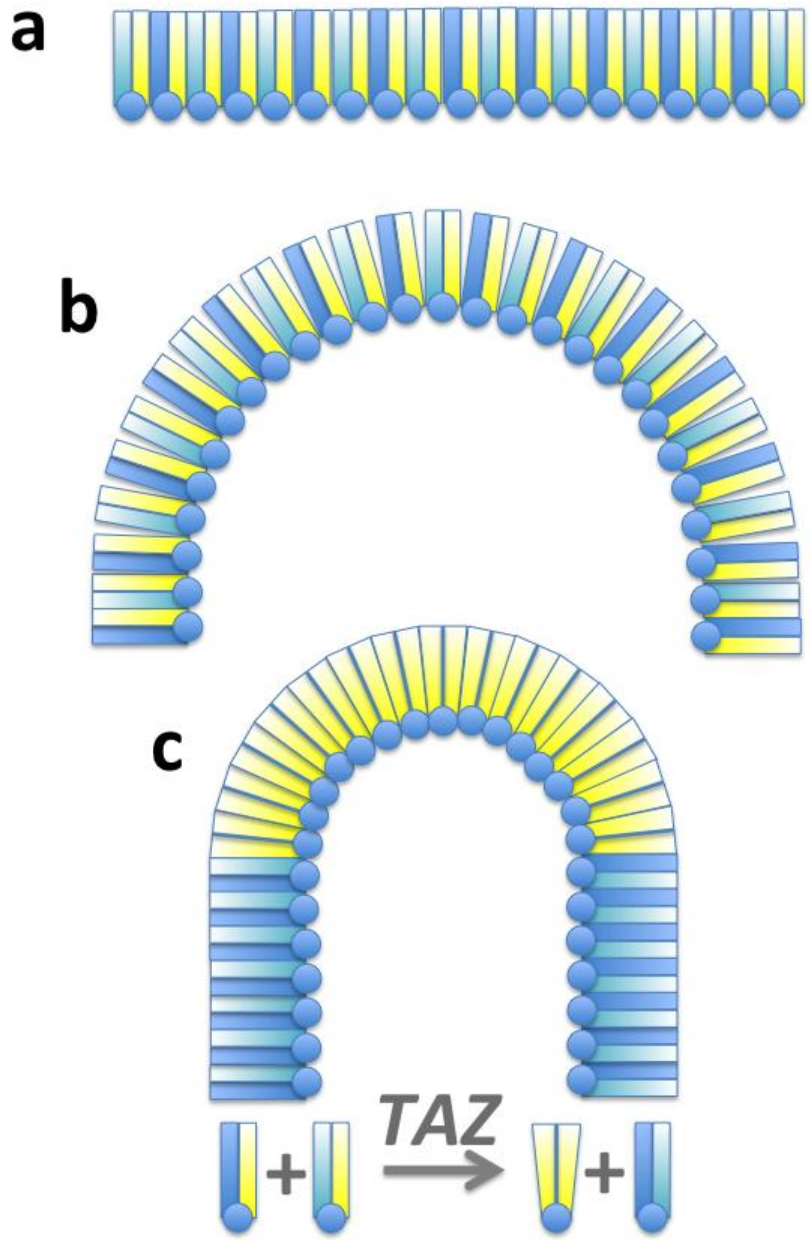




Conclusions II

- The acyl specificity of tafazzin depends on the lipid phase state.

- Native molecular species of cardiolipin can be created in vitro if tafazzin reacts with mitochondrial lipids in the hexagonal state.


a
b
c
TAZ
+
+

Acknowledgements

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Mindong Ren
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NYU School of Medicine

Richard Epand
Bob Berno

McMaster University

^{31}P NMR