EAGLE CLINICAL®

Resolving the Gap

SPMs and PEA as the missing half of your Inflammation Strategy

Nathan Rose – BHSc(Nat)
Head of Education - Integria

SPECIALISED NUTRITIONAL MEDICINE

Everyone is talking about Inflammation

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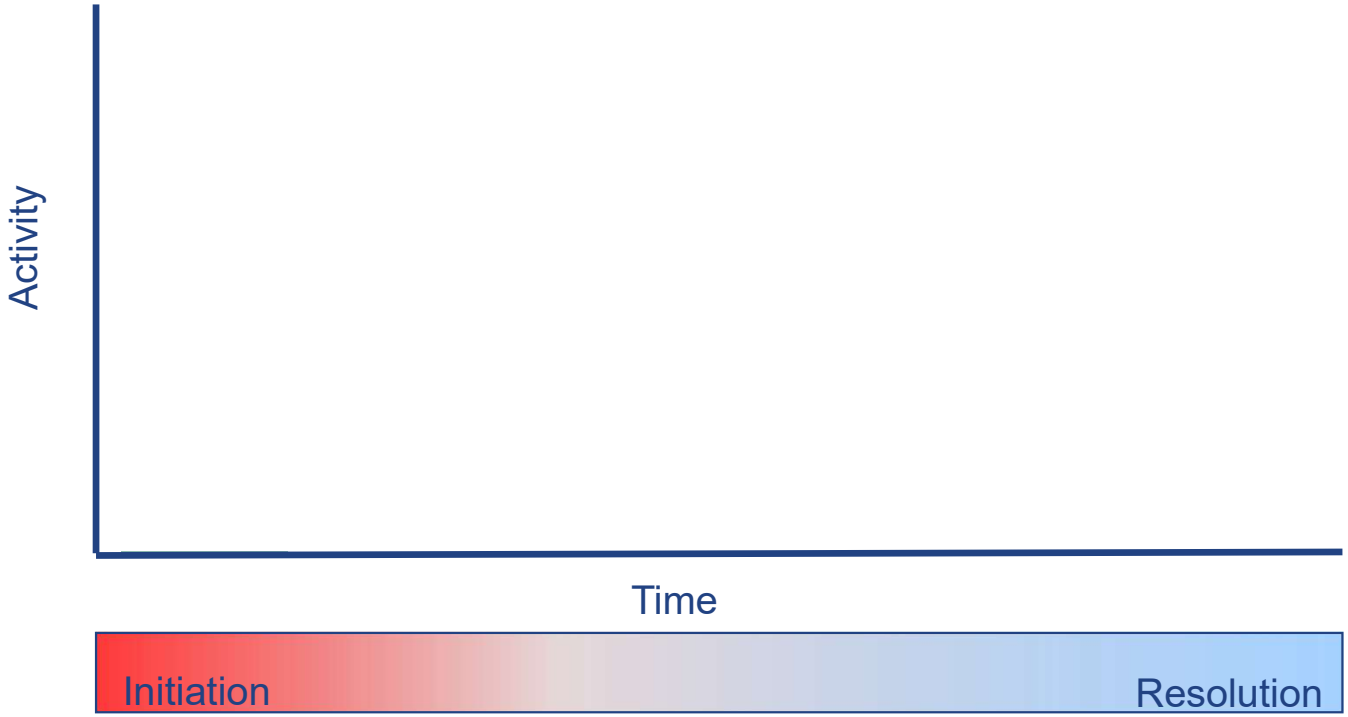
Resolution is a separate and active process



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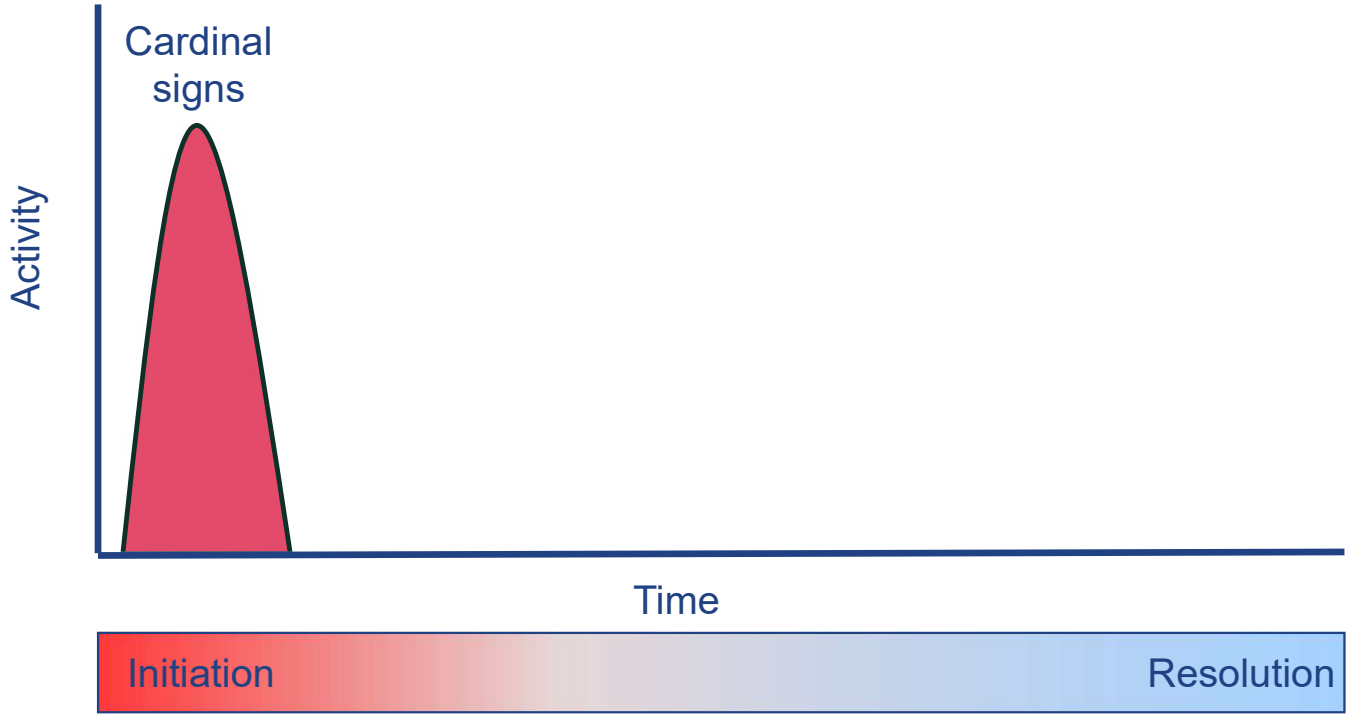

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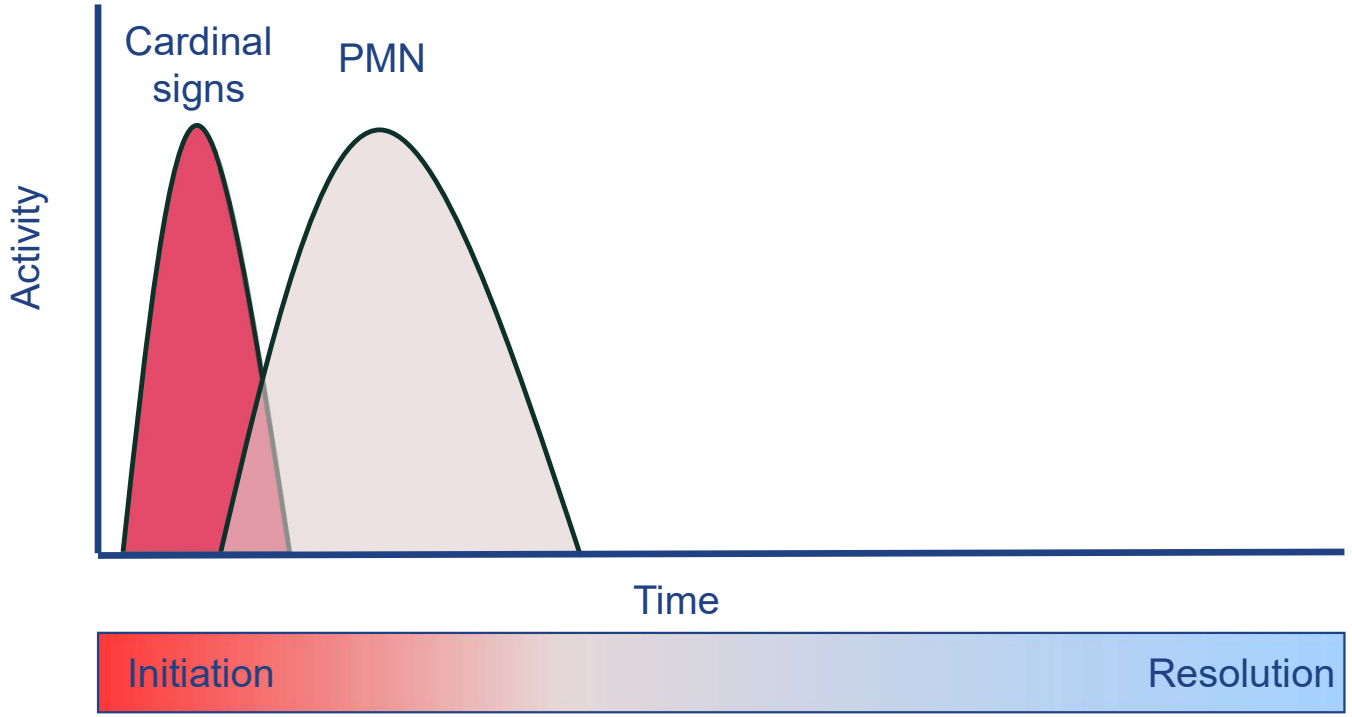

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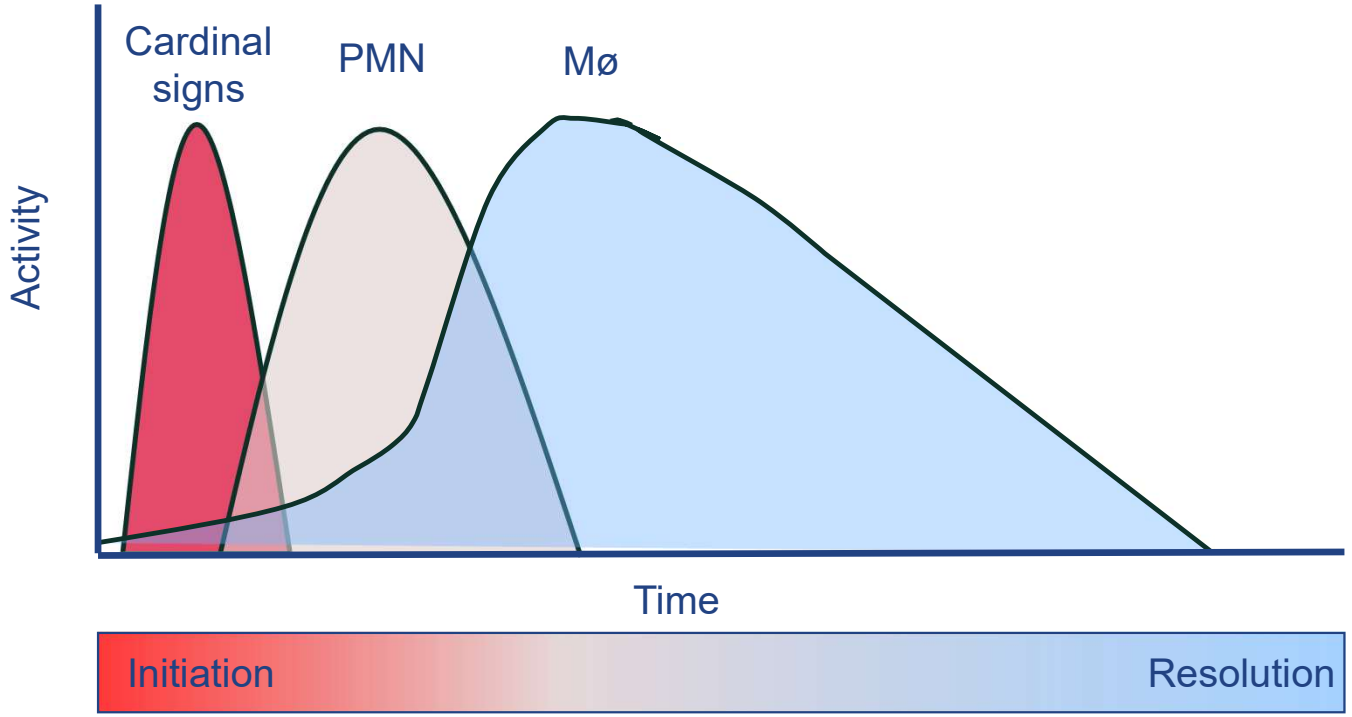

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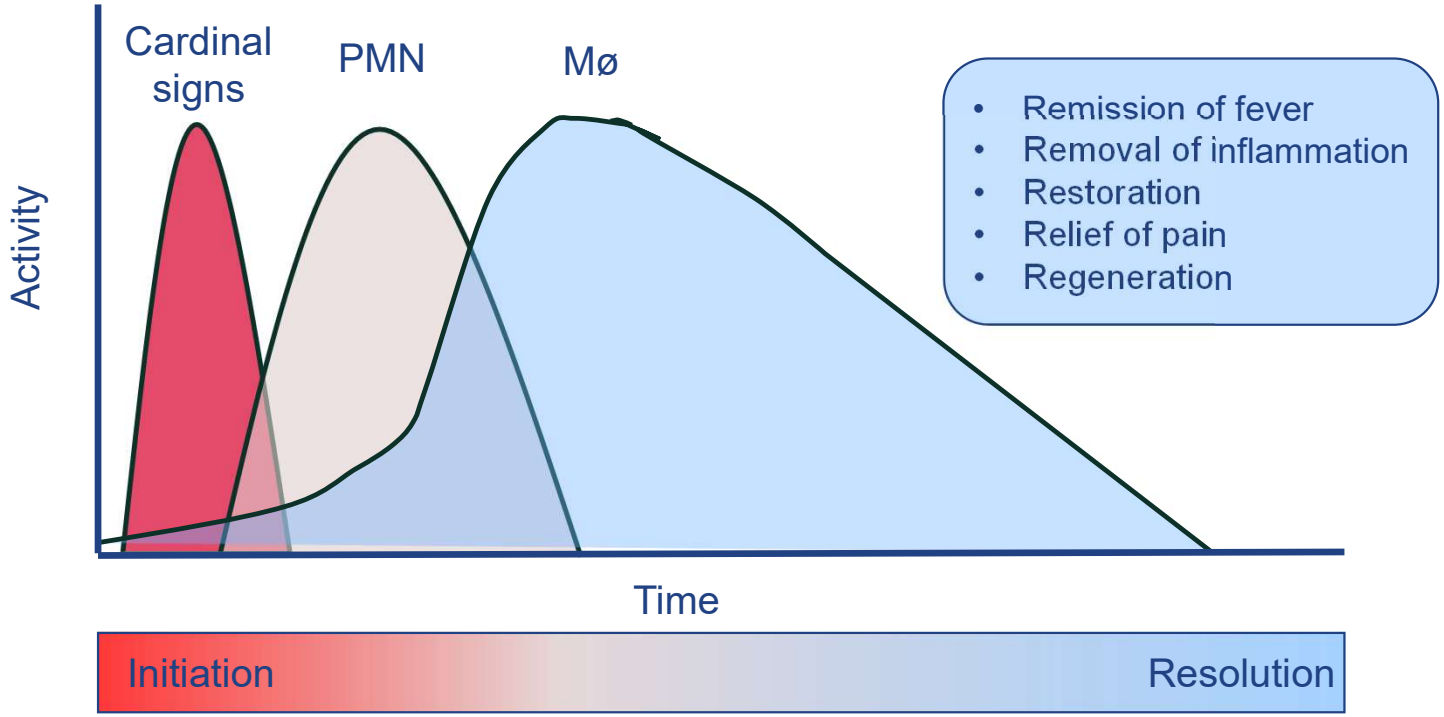

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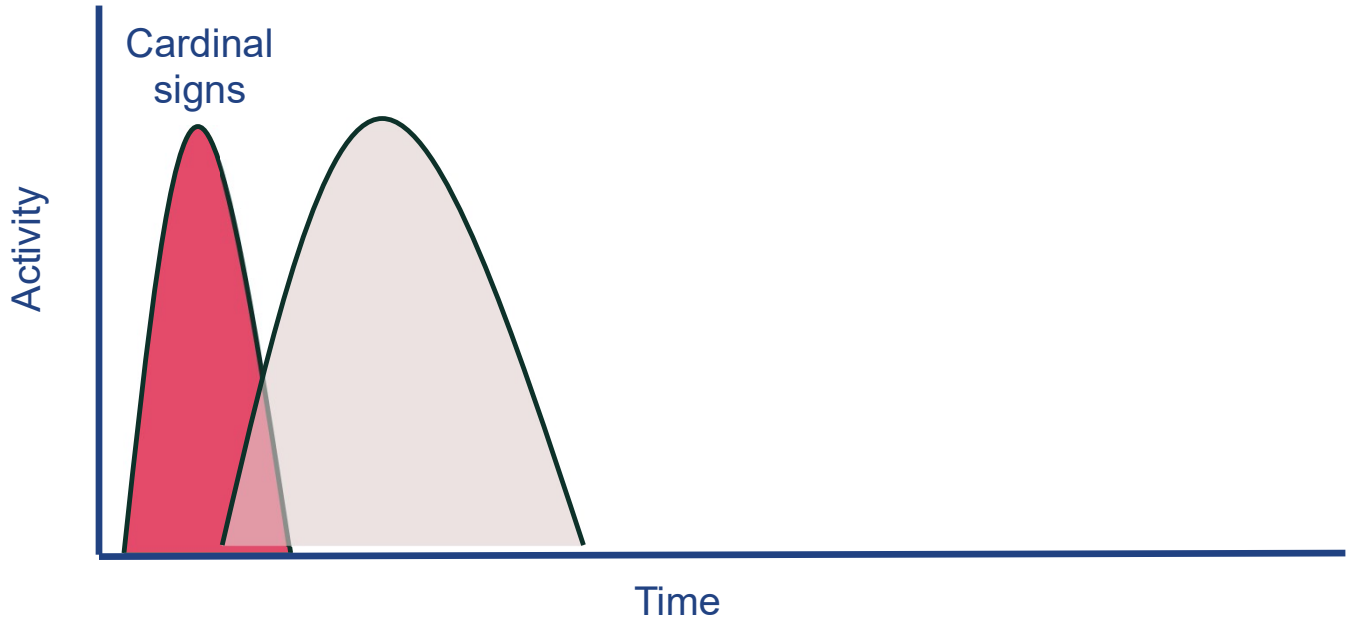
Inflammation versus resolution



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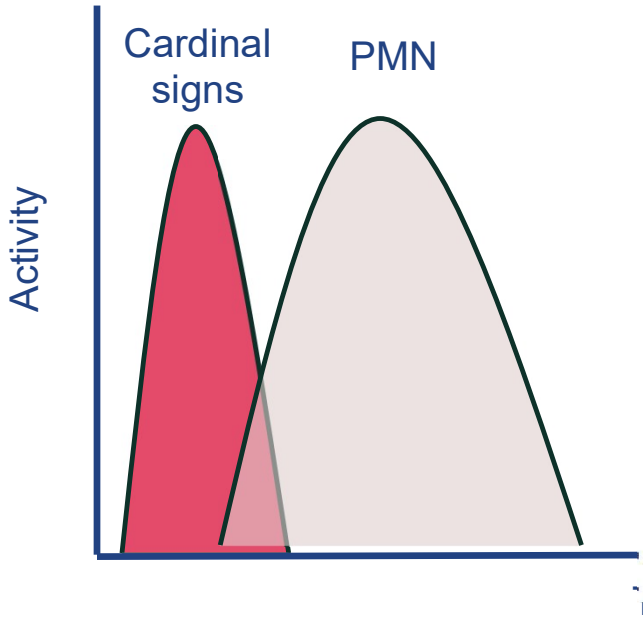

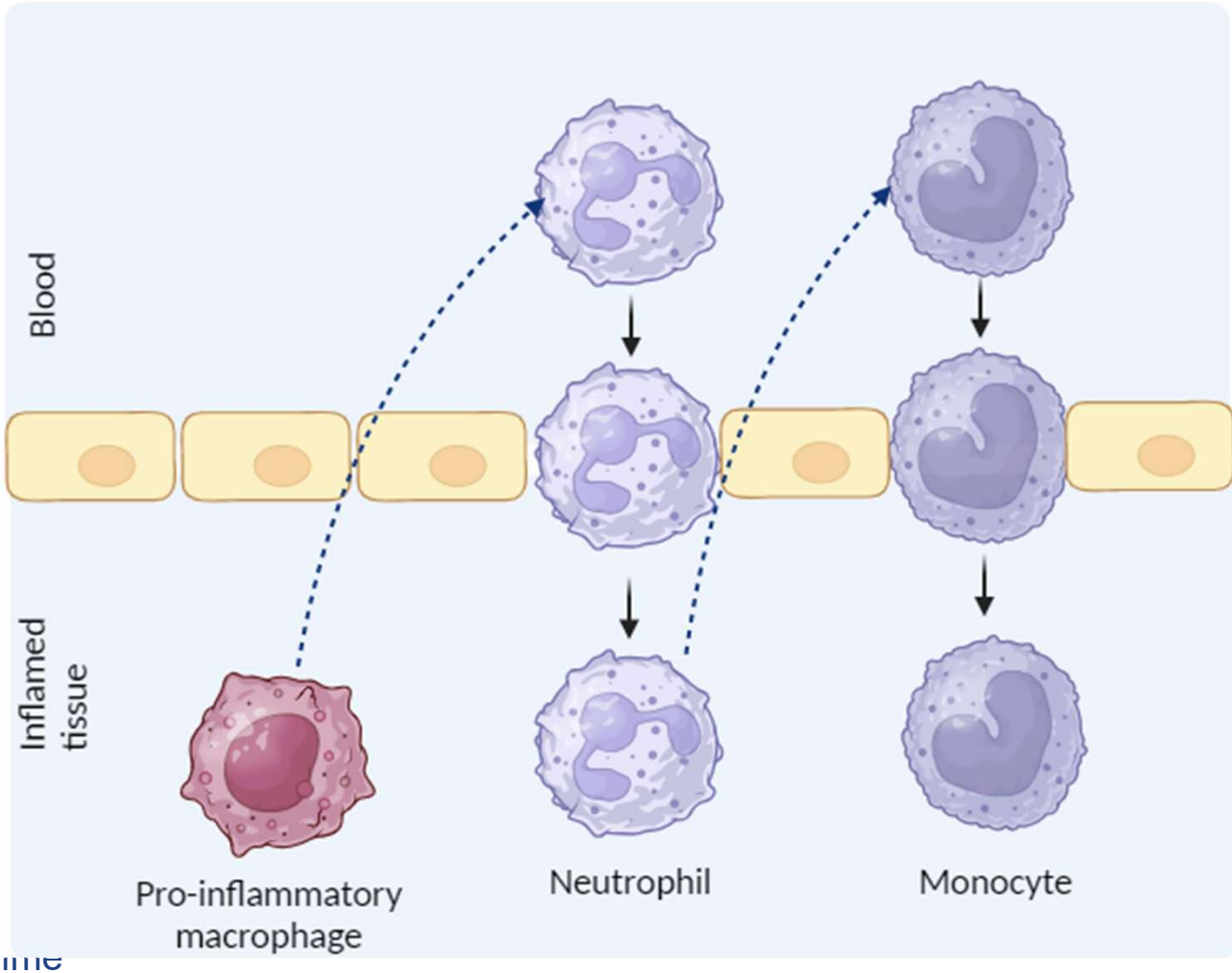

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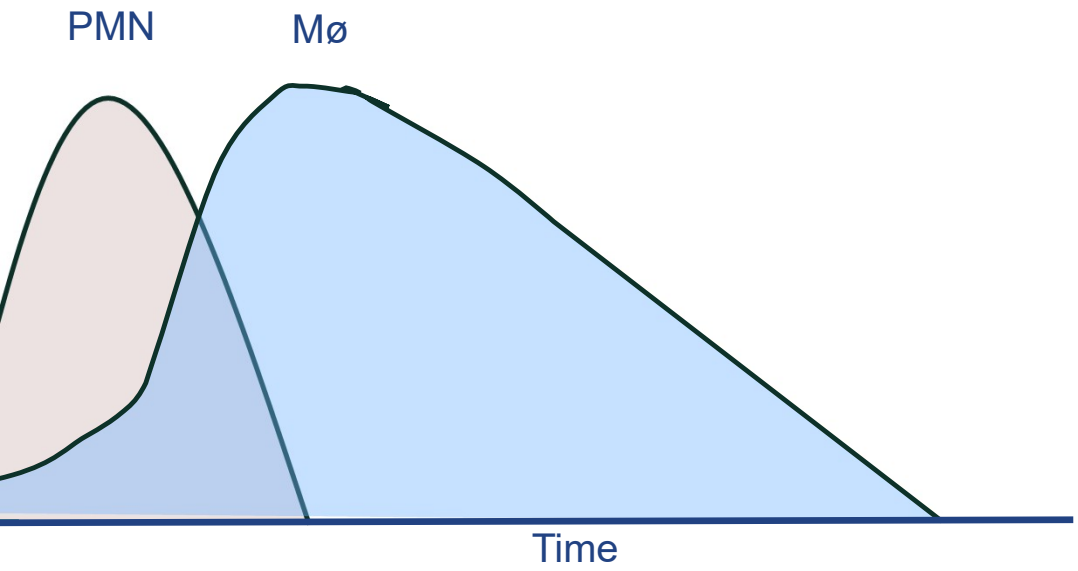

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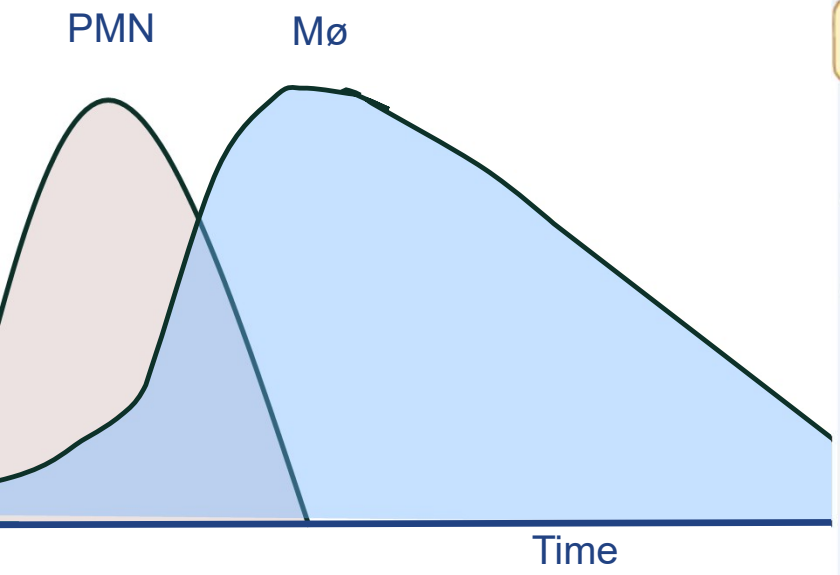

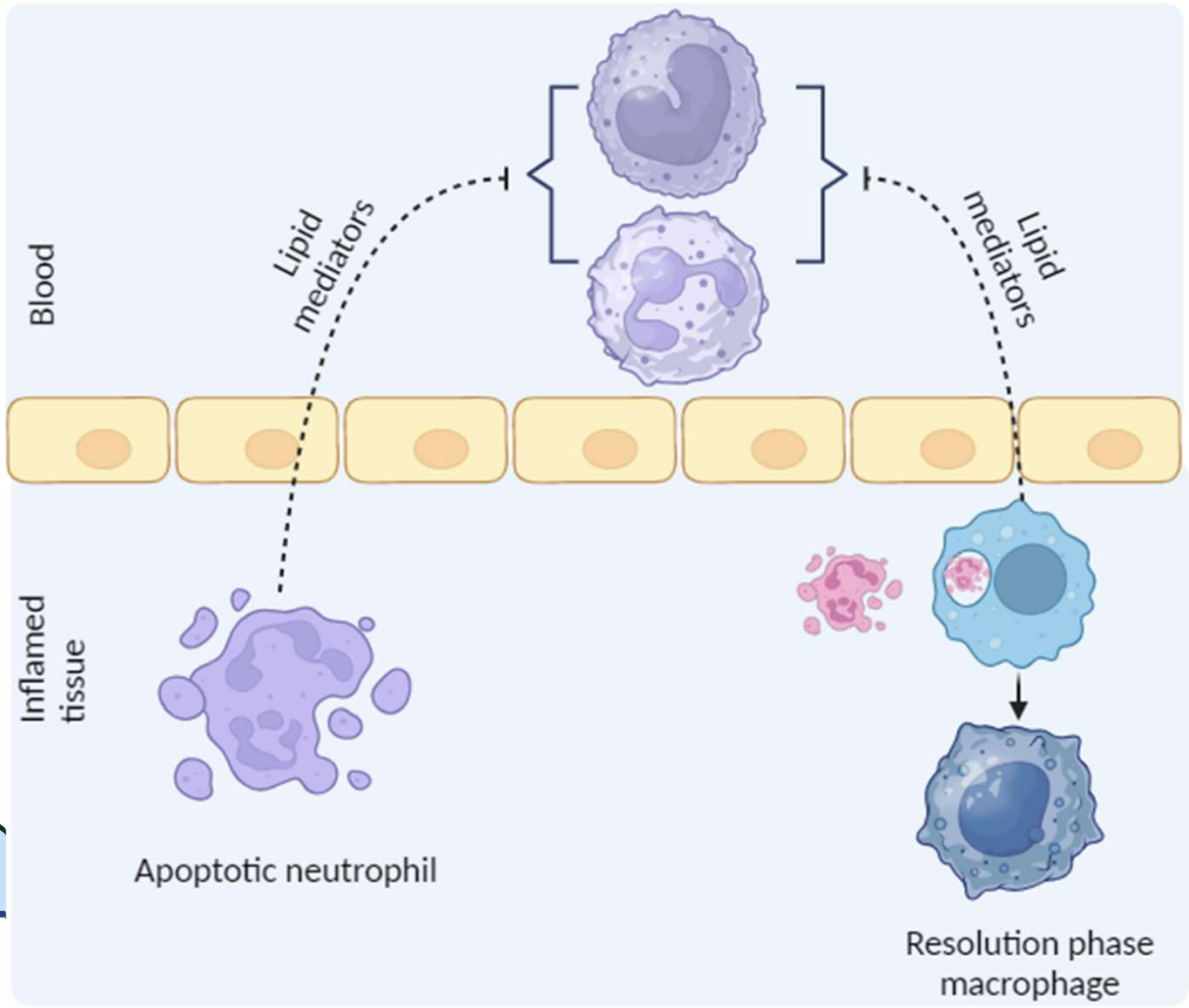

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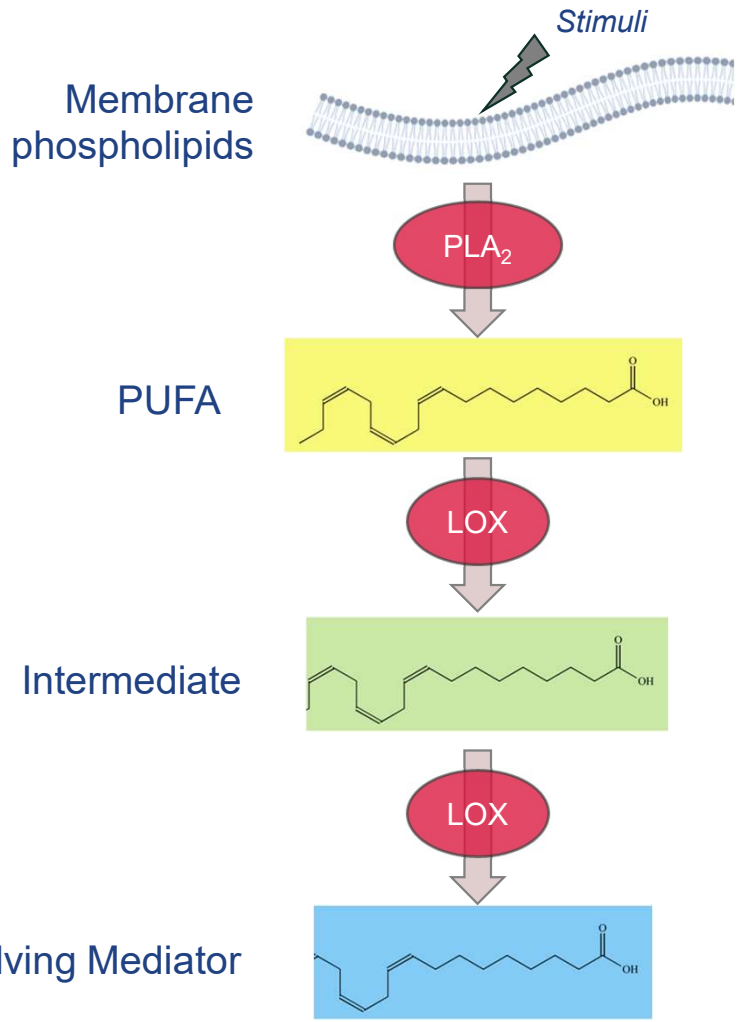
Lipid mediators stimulate resolution



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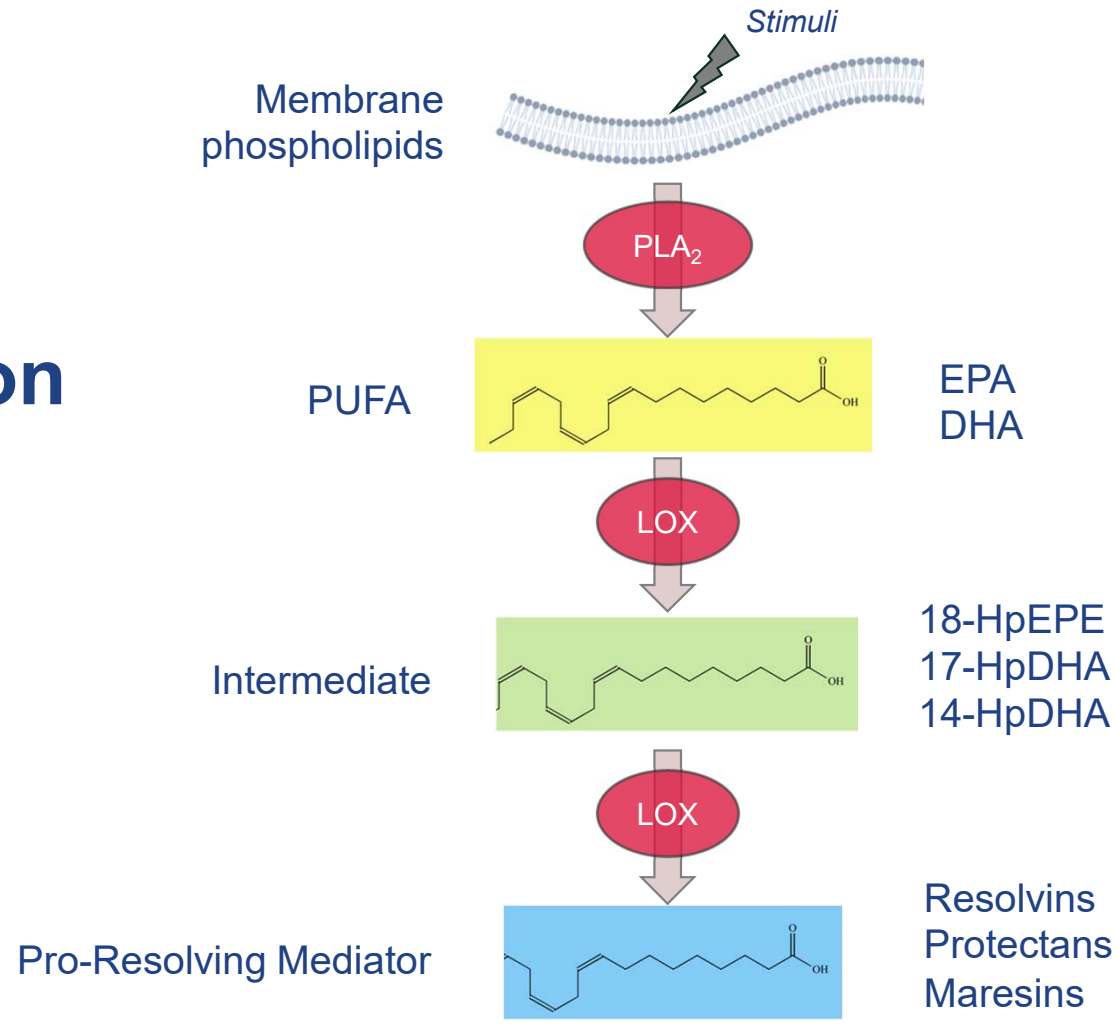

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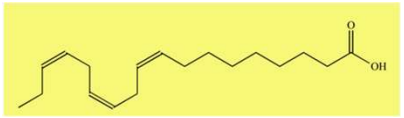
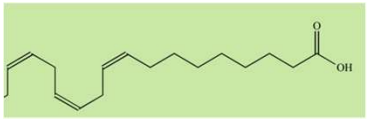
PUFA



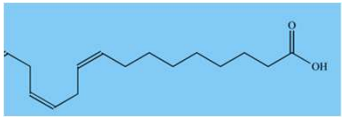
EPA
DHA

Intermediate



18-HpEPE
17-HpDHA
14-HpDHA

Pro-Resolving Mediator



Resolvins
Protectans
Maresins

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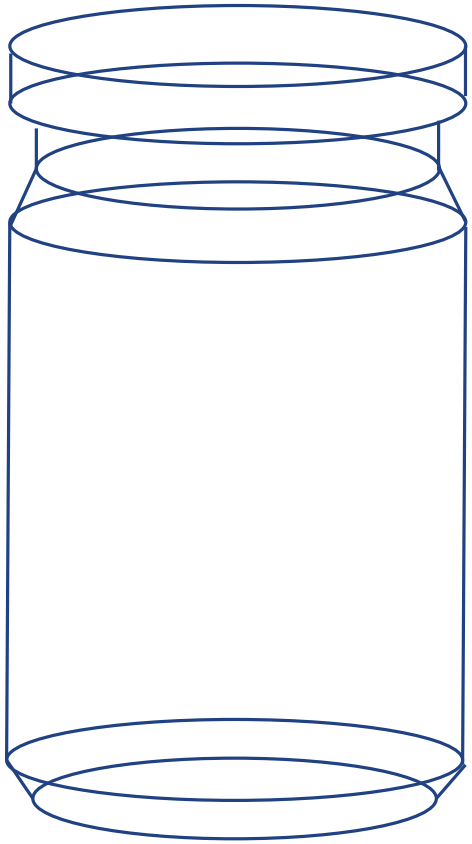
FISH OIL



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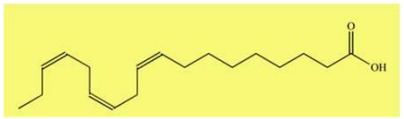

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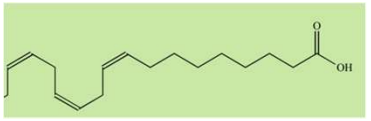

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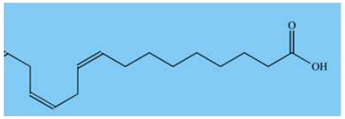

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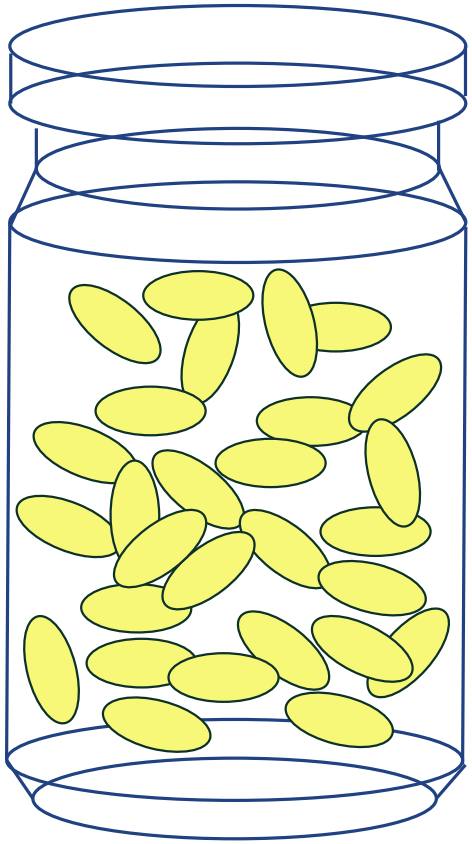

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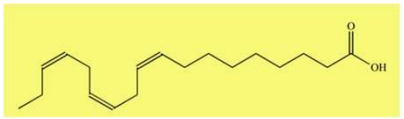

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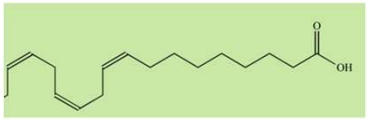

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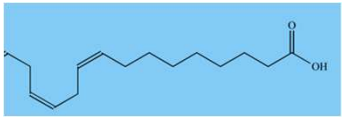

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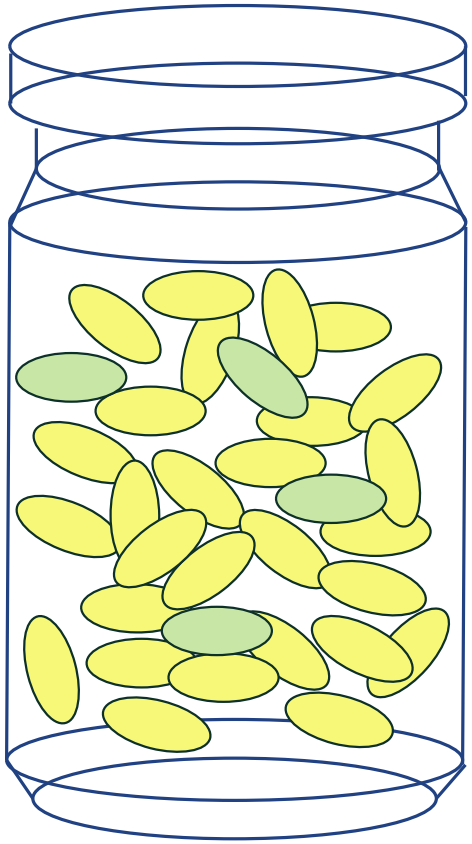

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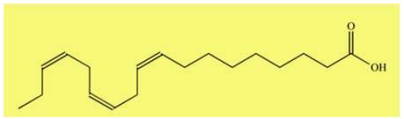

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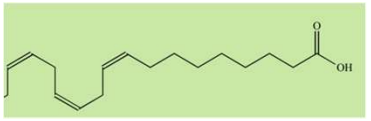

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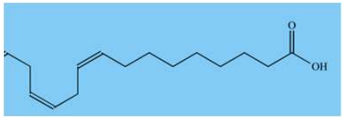

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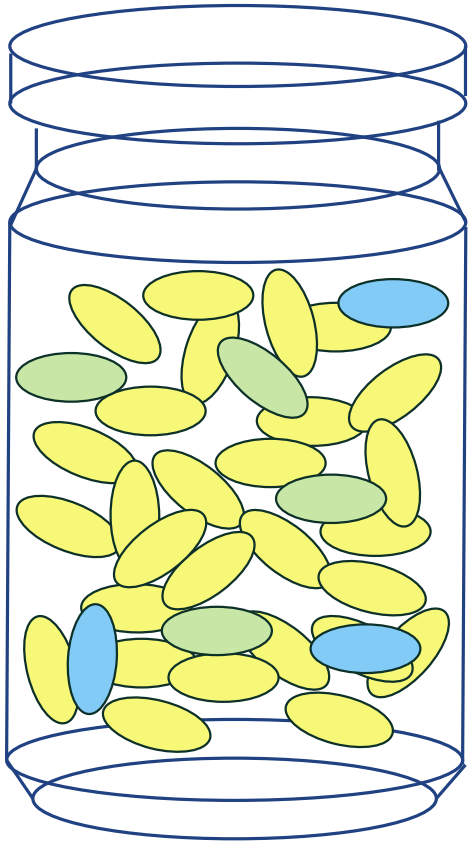

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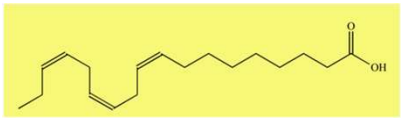

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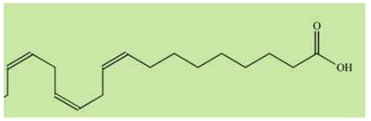

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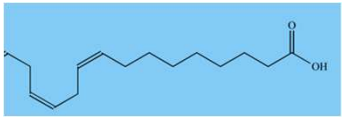

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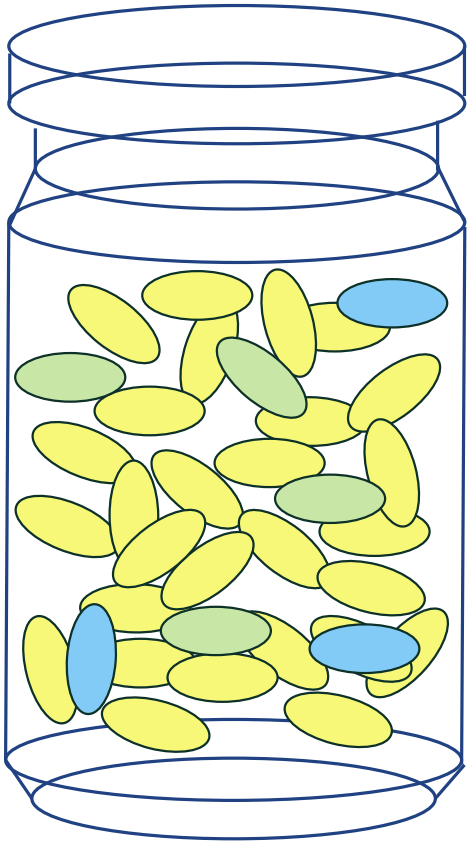

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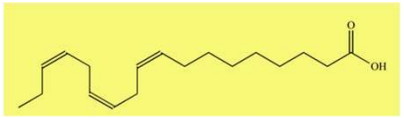

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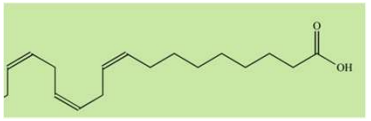

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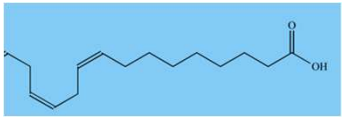

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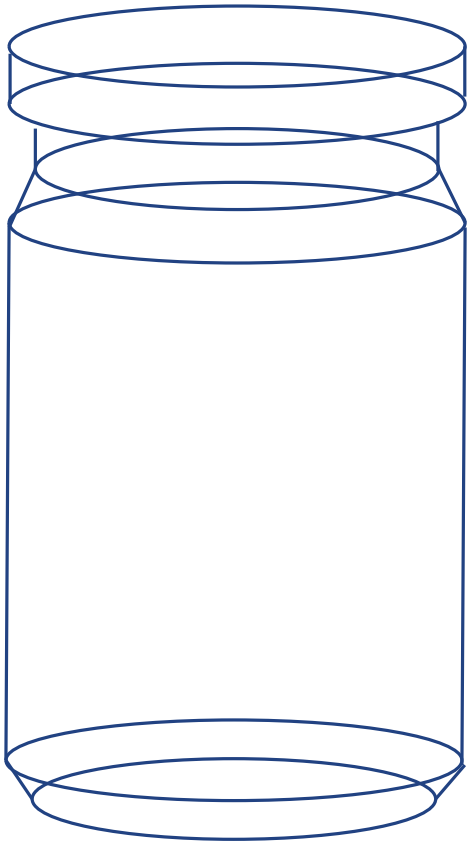

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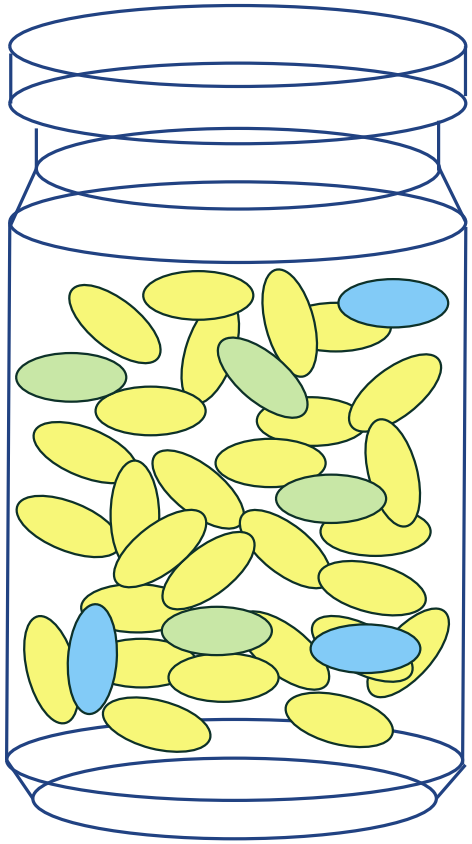

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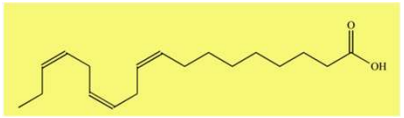

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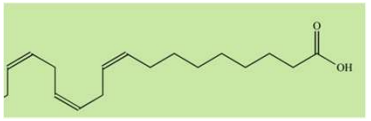

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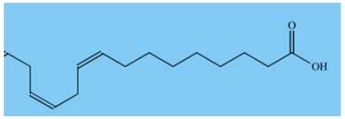

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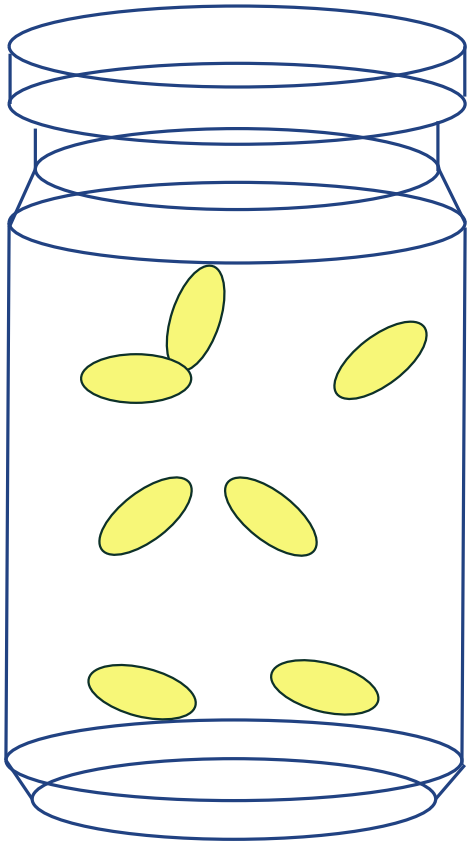

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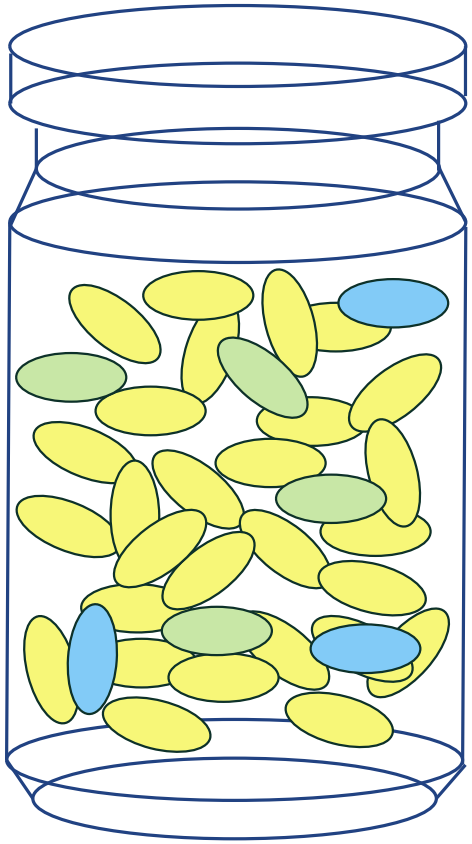

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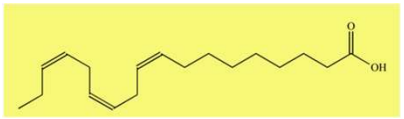

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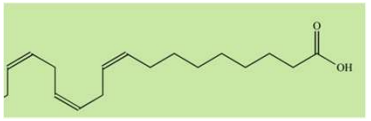

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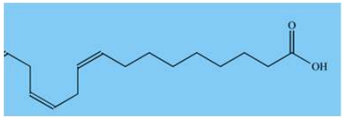

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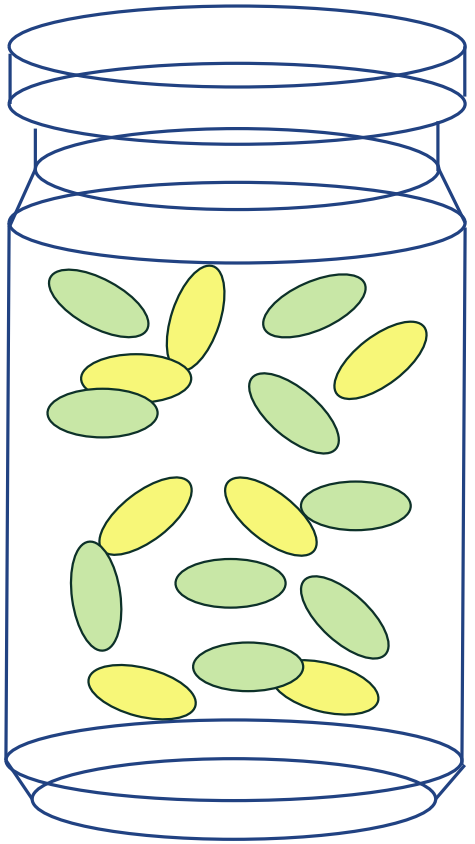

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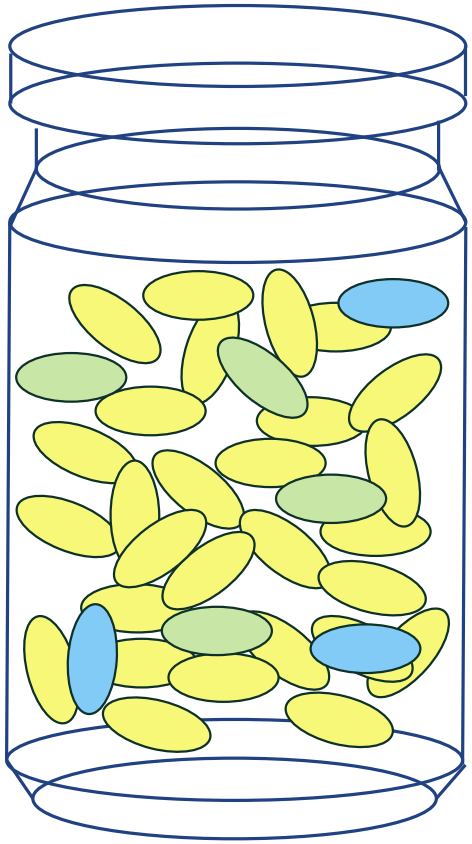

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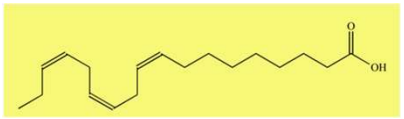

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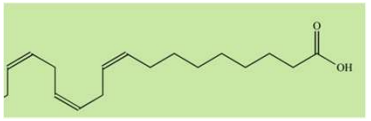
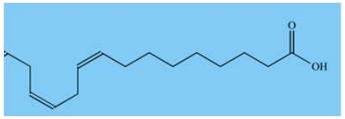
Intermediate



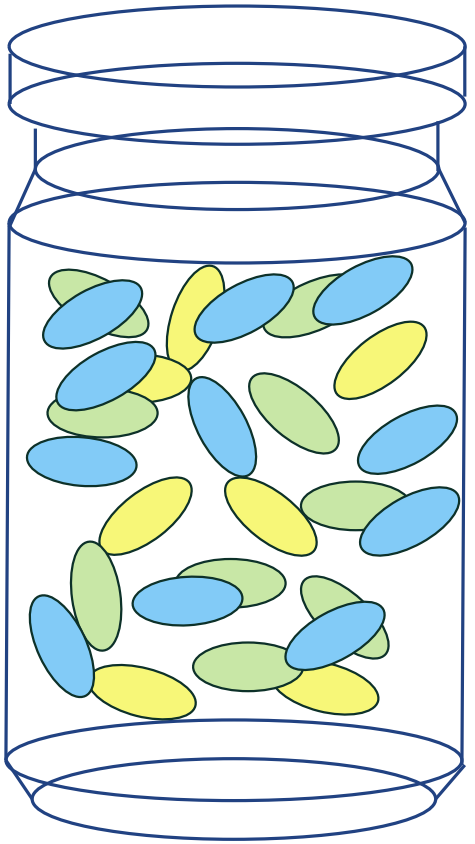
18-HpEPE
17-HpDHA
14-HpDHA

Pro-Resolving Mediator



Resolvins
Protectans
Maresins

SPMs



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Low SPM Levels

Diabetes
Obesity

Multiple sclerosis
Inflammatory bowel disease
Rheumatoid arthritis

Osteoarthritis
Chronic Pain

COVID-19
Rhinosinusitis

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Impaired SPM biosynthesis

Smoking
Age

Sex

NSAID use

Surgery

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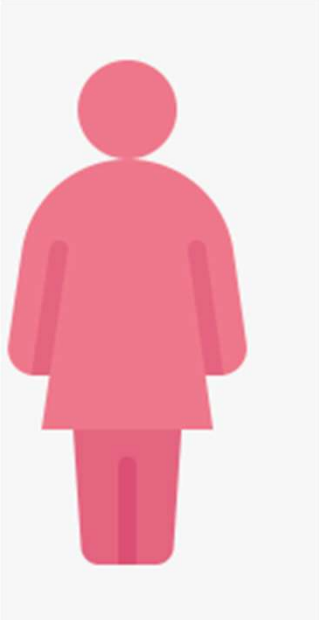
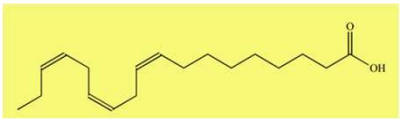
Female		Male
64	AGE	59
32.2	BMI	32.2
4.5	CRP (ug/ml)	4.7

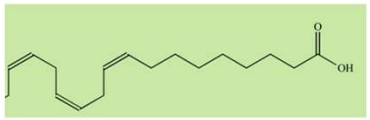


PUFA



EPA
DHA

Intermediate



18-HpEPE
17-HpDHA
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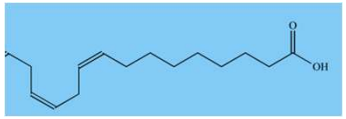
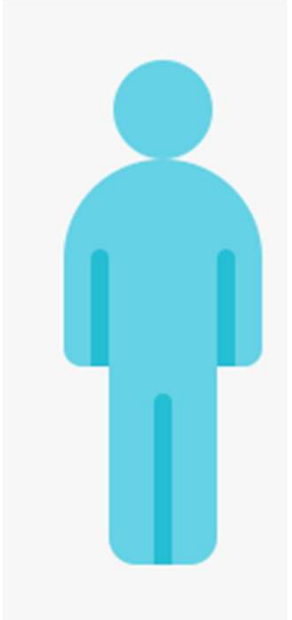
Pro-Resolving Mediator



Resolvins
Protectans
Maresins



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So J, et al. Sex differences in lipid mediators derived from omega-3 fatty acids in older individuals with low-grade chronic inflammation. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2024 Apr 1;203:102655.

Female		Male
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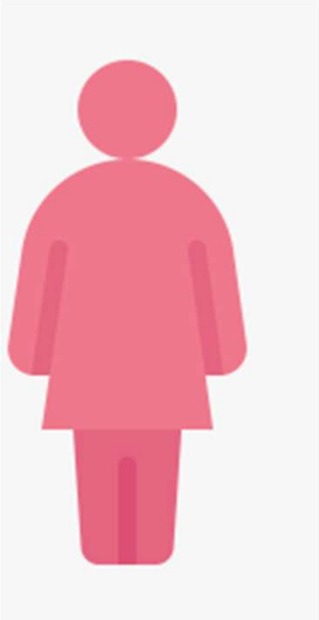
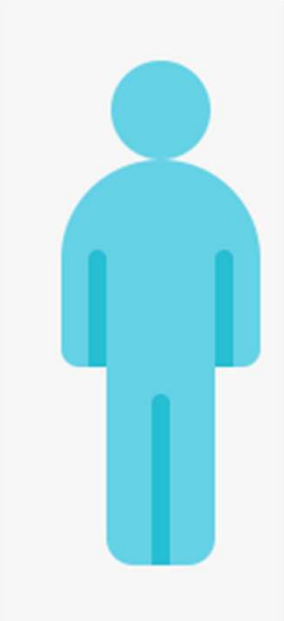


EPA
DHA

18-HpEPE
17-HpDHA
14-HpDHA

Resolvins
Protectans
Maresins



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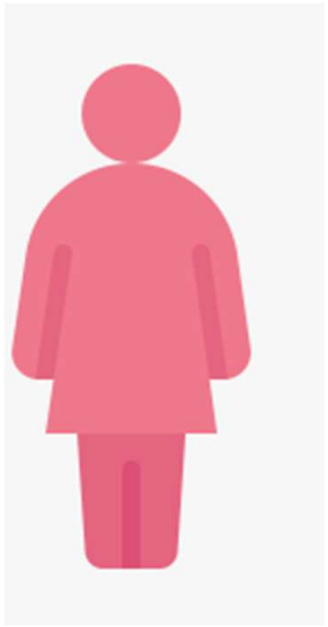
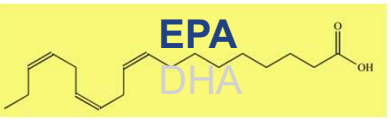


3g

EPA

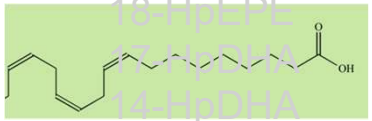
DHA



18-HpEPE

17-HpDHA

14-HpDHA

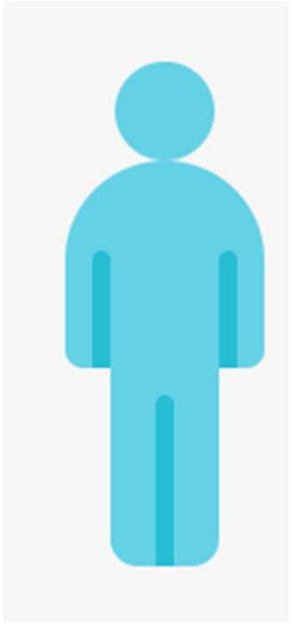


Resolvins

Protectans

Maresins

3g



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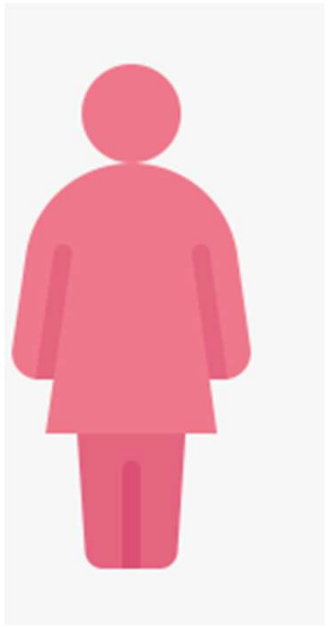
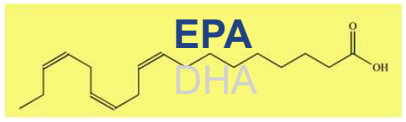
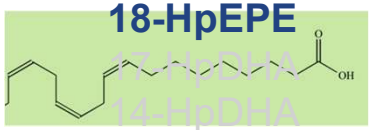


3g

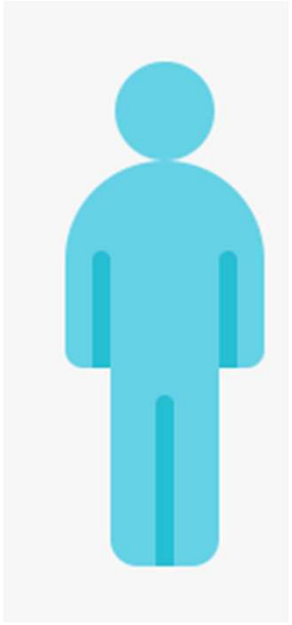
89 (pg/ml)





3g

136 (pg/ml)



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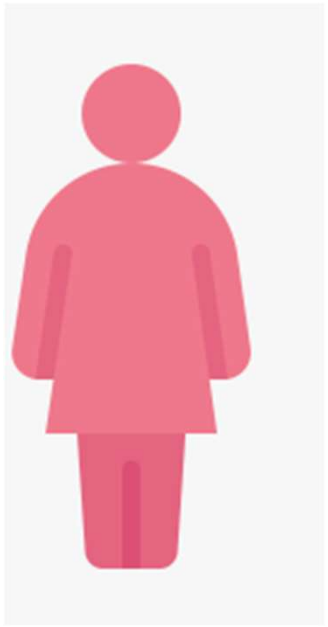
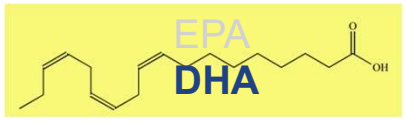
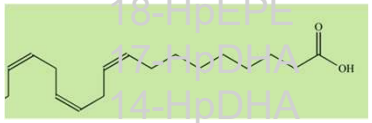
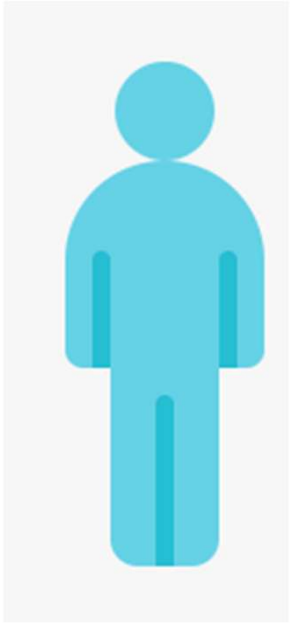


3g





3g



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Male

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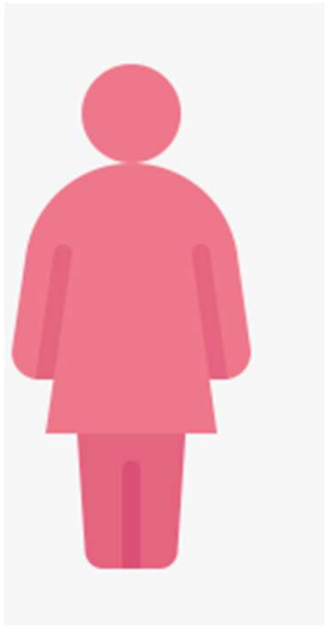
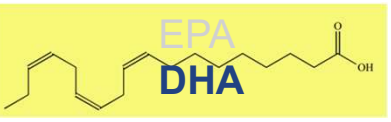
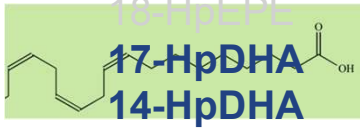
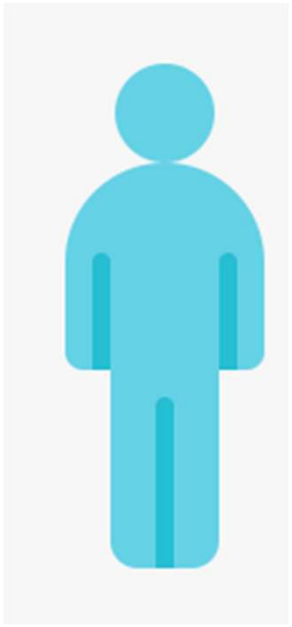


3g	EPA DHA	3g
28 pg/ml 496 pg/ml	18-HpEPE 17-HpDHA 14-HpDHA	51 pg/ml 961 pg/ml
	Resolvins Protectans Maresins	







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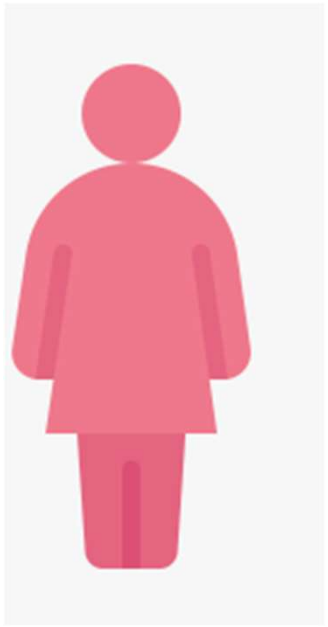

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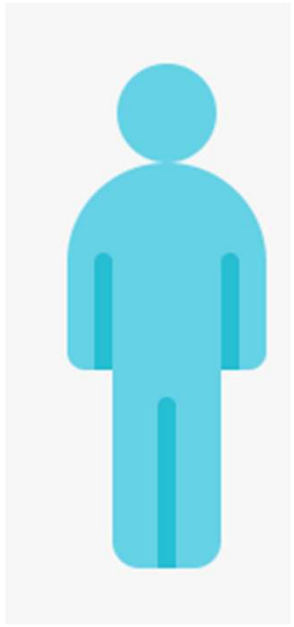

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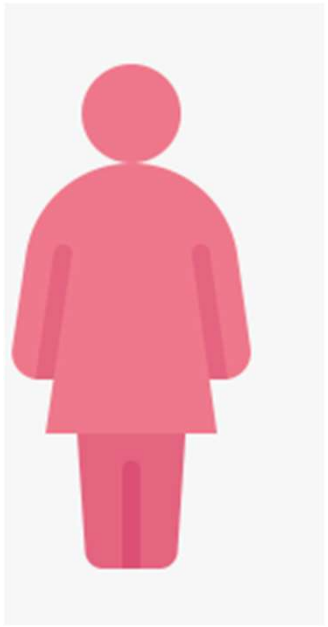
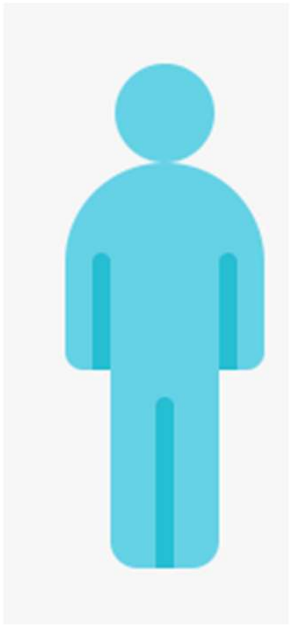


3g	EPA DHA	3g
28 pg/ml 496 pg/ml	18-HpEPE 17-HpDHA 14-HpDHA	51 pg/ml 961 pg/ml
-64 pg/ml 22 pg/ml	Resolvins: RvD1 RvD5	10 pg/ml 32 pg/ml



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Fish oils versus SPMs

PUFA

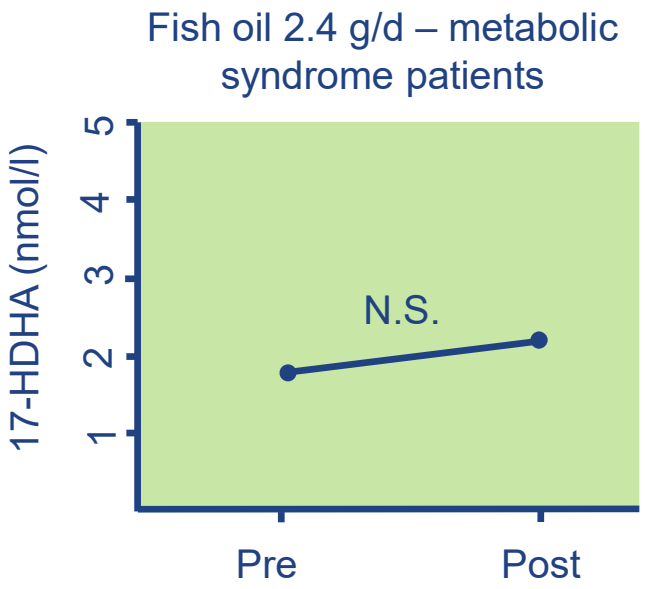
EPA
DHA

Intermediate

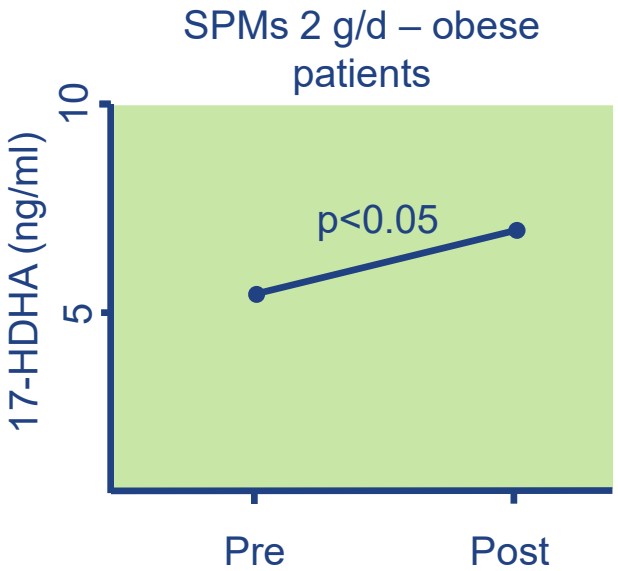
18-HpEPE
17-HpDHA
14-HpDHA

Pro-Resolving Mediator

Resolvins
Protectans
Maresins



Barden AE, et al.Am J Clin Nutr. 2015 Dec;102(6):1357-64



Al-Shaer AE et al. J Nutr. 2022 Jul 6;152(7):1783-1791.

EAGLE CLINICAL®

Fish oils versus SPMs

PUFA

EPA
DHA

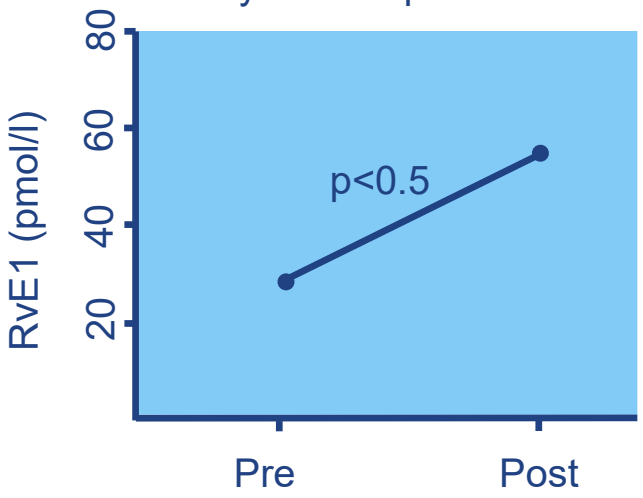
Intermediate

18-HpEPE
17-HpDHA
14-HpDHA

Pro-Resolving Mediator

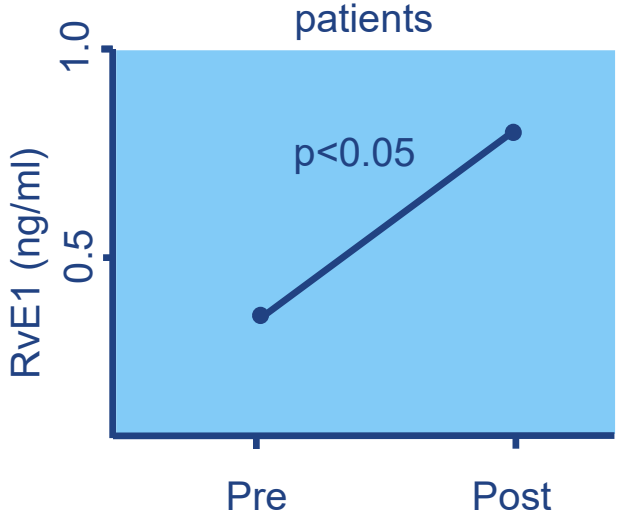
Resolvins
Protectans
Maresins

Fish oil 2.4 g/d – metabolic syndrome patients



Barden AE, et al.Am J Clin Nutr. 2015 Dec;102(6):1357-64

SPMs 2 g/d – obese patients



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Fish oils versus SPMs

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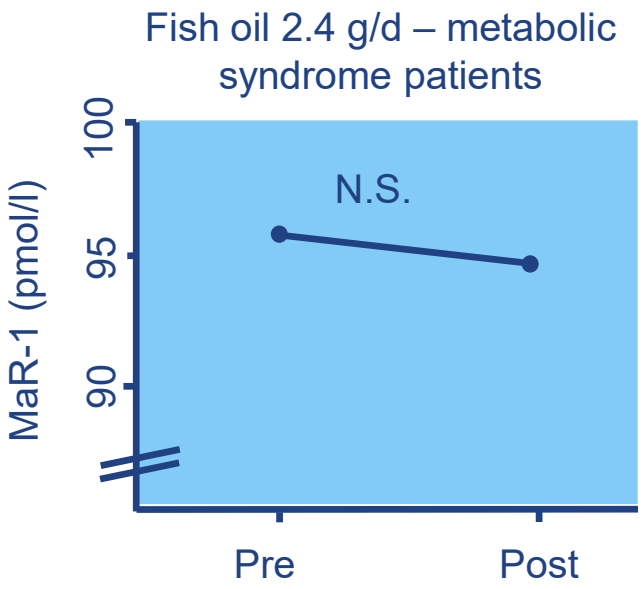

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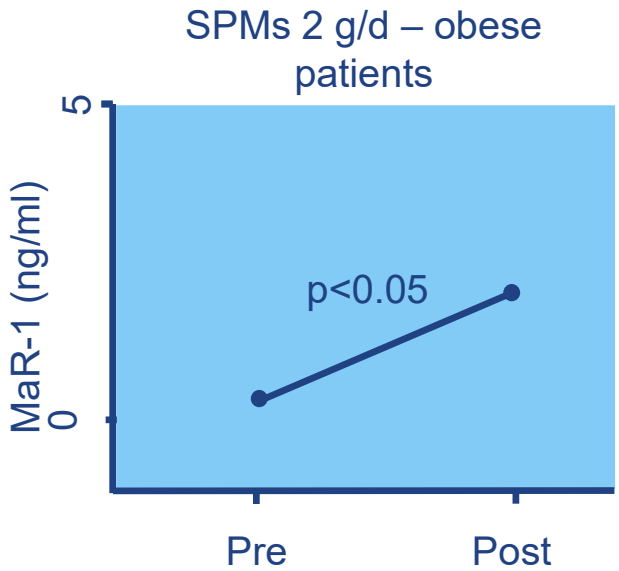

Al-Shaer AE et al. J Nutr. 2022 Jul 6;152(7):1783-1791.

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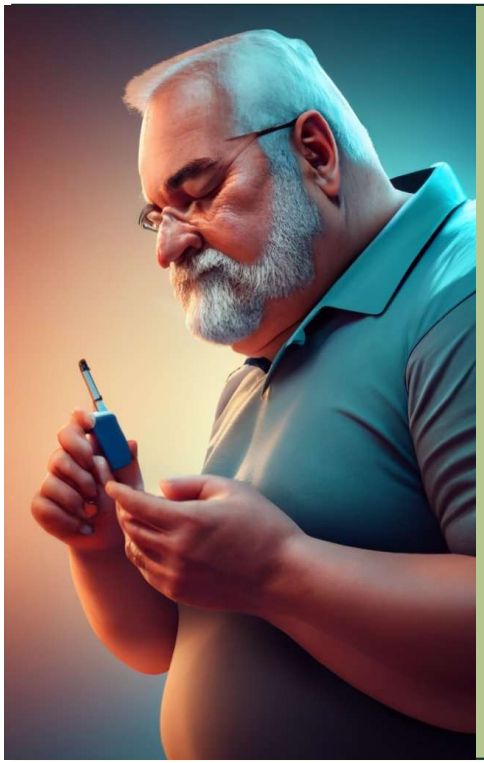
When to consider

Fish oil

- Low EPA/DHA intake
- Pregnancy
- Children
- Cardiovascular risk
- First line therapy



SPMs

- Older patient
- Obesity & metabolic dysfunction
- Pain disorders
- Autoimmune
- Chronic infection
- Unresponsive to fish oil

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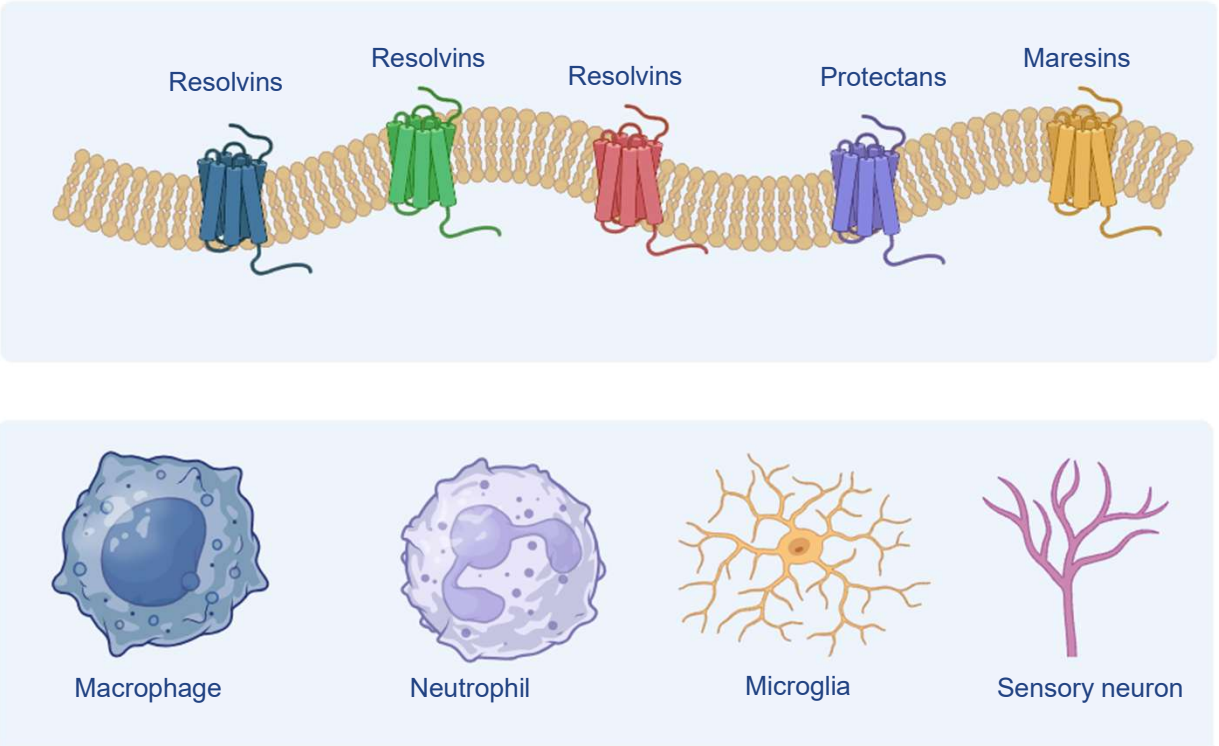
SPMs carry out their actions through GPCR receptors



EAGLE CLINICAL®

Ji RR. Specialized Pro-Resolving Mediators as Resolution Pharmacology for the Control of Pain and Itch. Annu Rev Pharmacol Toxicol. 2023 Jan 20;63:273-293. doi: 10.1146/annurev-pharmtox-051921-084047.

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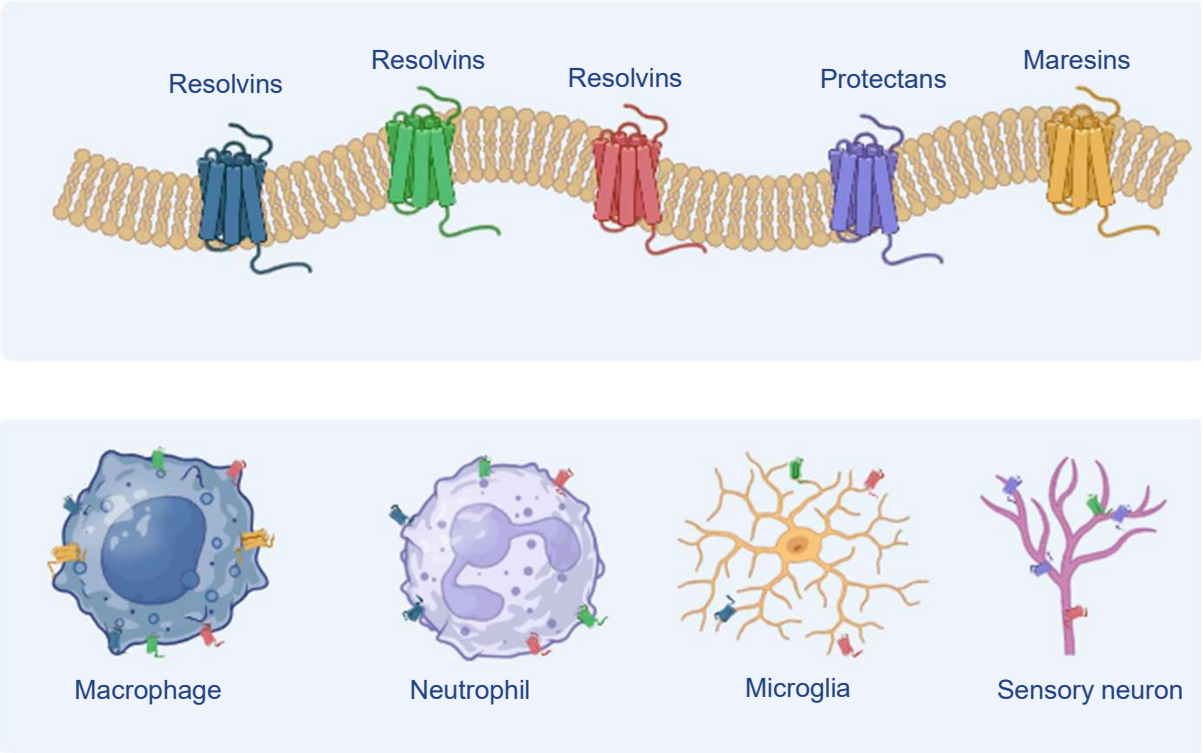

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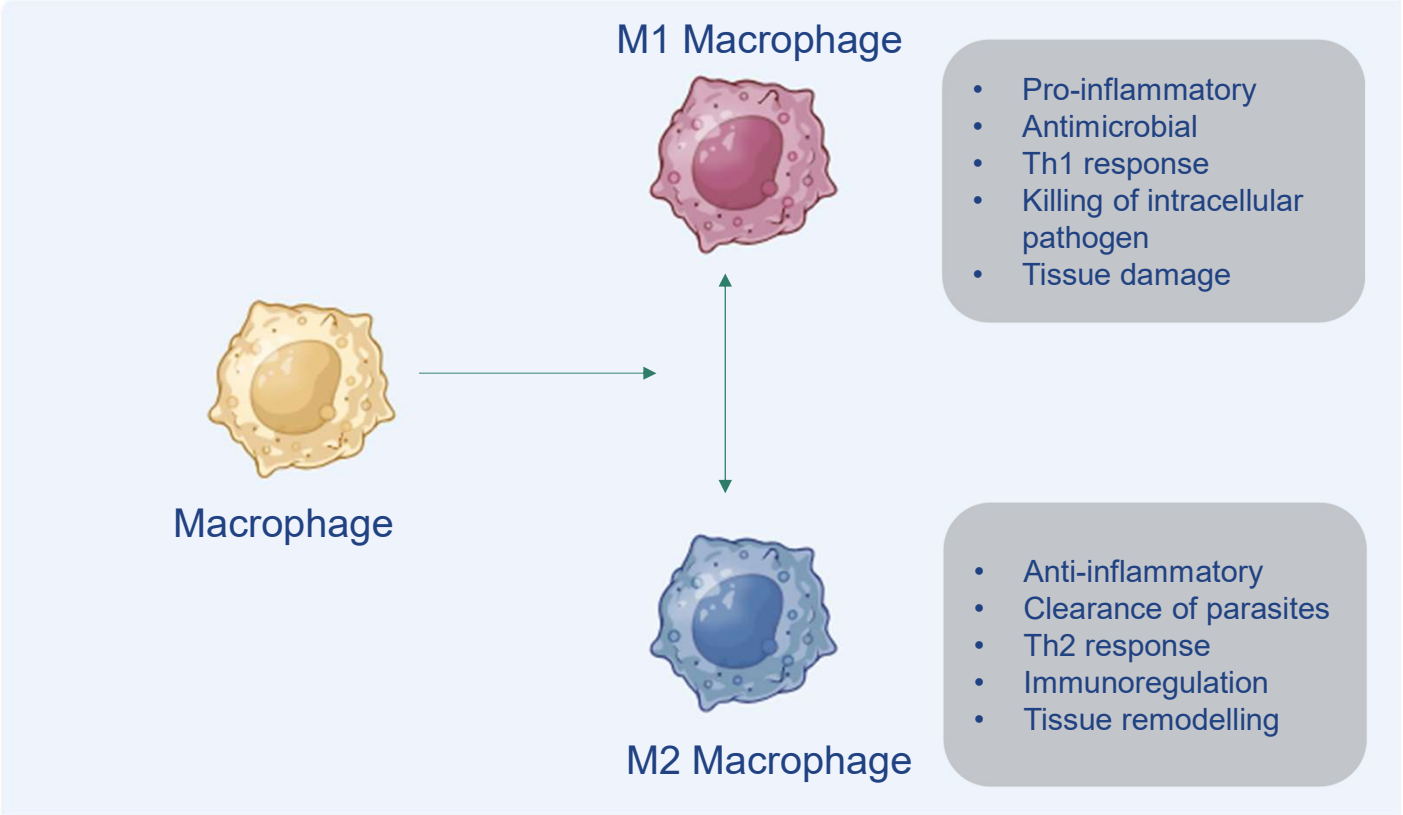
Macrophage polarisation



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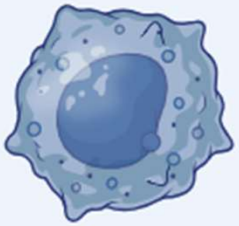
Saqib U, Sarkar S, Suk K, Mohammad O, Baig MS, Savai R. Phytochemicals as modulators of M1-M2 macrophages in inflammation. Oncotarget. 2018 Apr 3;9(25):17937-17950. doi: 10.18632/oncotarget

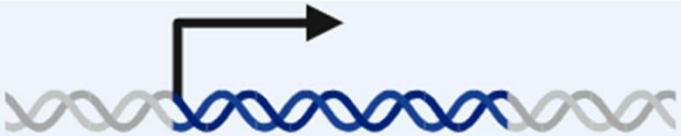
SPMs promote resolution physiology



↑ bacterial phagocytosis

↑ bacterial phagocytosis

↓ adhesion

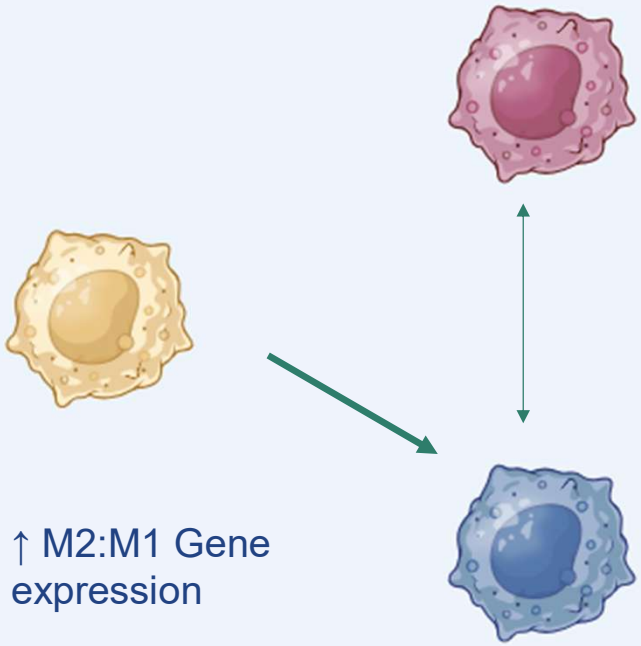


Δ genes: immune response, leukocyte recruitment and cellular metabolism

- 1, 3, or 4.5 g dose or placebo
- Healthy individuals
- 24-hour measurement

Souza PR, Marques RM, Gomez EA, Colas RA, De Matteis R, Zak A, Patel M, Collier DJ, Dalli J. Enriched Marine Oil Supplements Increase Peripheral Blood Specialized Pro-Resolving Mediators Concentrations and Reprogram Host Immune Responses: A Randomized Double-Blind Placebo-Controlled Study. Circ Res. 2020 Jan 3;126(1):75-90. doi: 10.1161/CIRCRESAHA.119.315506

SPMs promote resolution physiology



↑ M2:M1 Gene expression

↑ bacterial phagocytosis

↓ adhesion
↓ leukocyte infiltration

- 1.5, 3.0, 6.0 g
- 10 Healthy individuals
- 10 Peripheral arterial disease
- 5-day treatment

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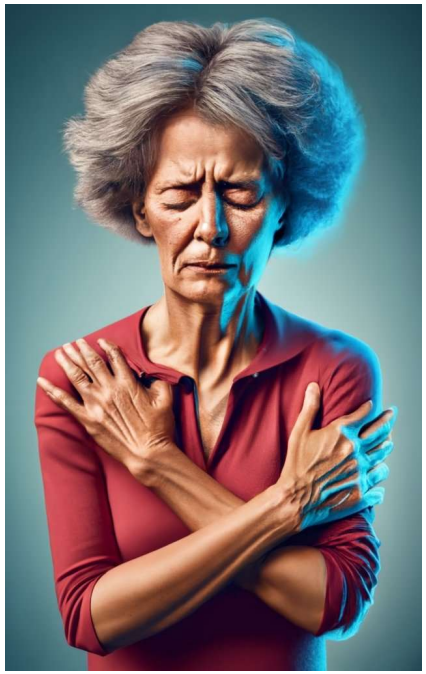
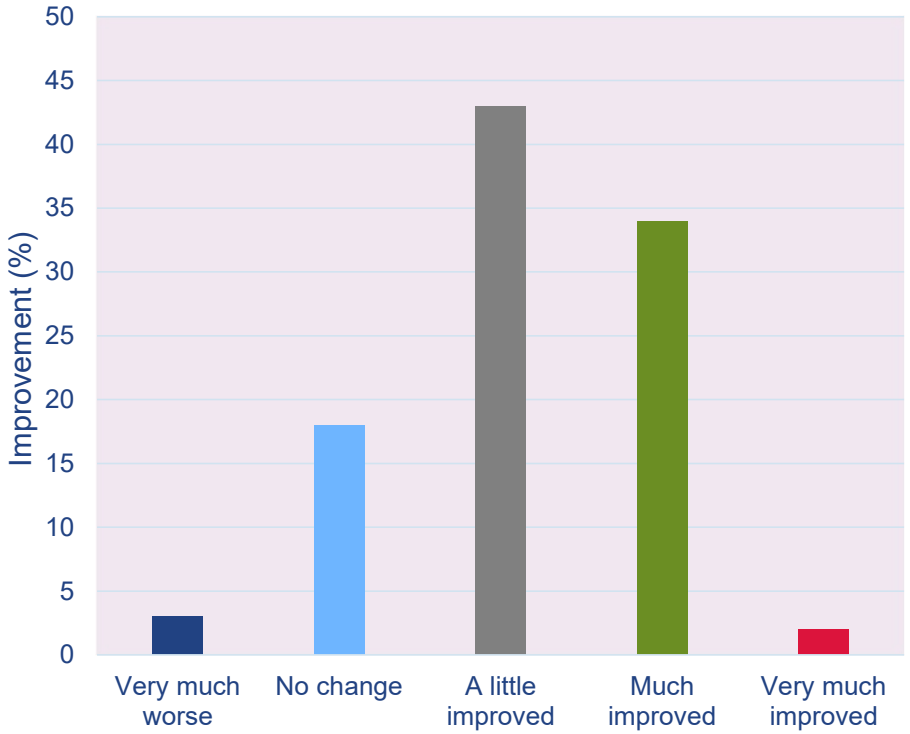
Schaller MS, et al. Treatment With a Marine Oil Supplement Alters Lipid Mediators and Leukocyte Phenotype in Healthy Patients and Those With Peripheral Artery Disease. J Am Heart Assoc. 2020 Aug 4;9(15):e016113. doi: 10.1161/JAHA.120.016113.

SPMs reduce pain



- 1.5 - 3 g/day
- 4 weeks
- 44 pain patients

- ↓ Pain
- ↑ QOL
- ↑ Mood
- ↑ Sleep
- ↓ Fatigue
- ↑ Physical function



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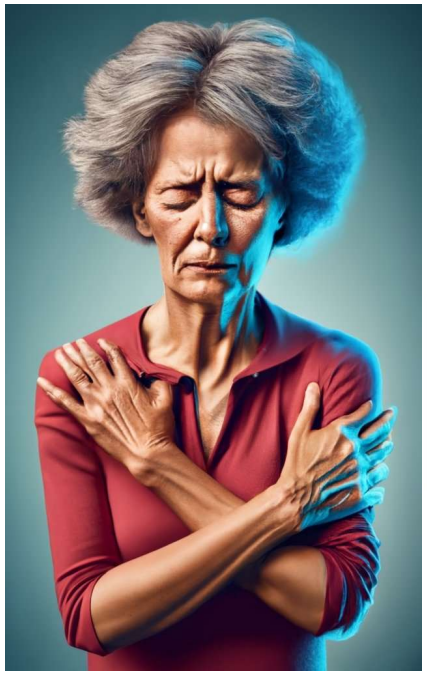
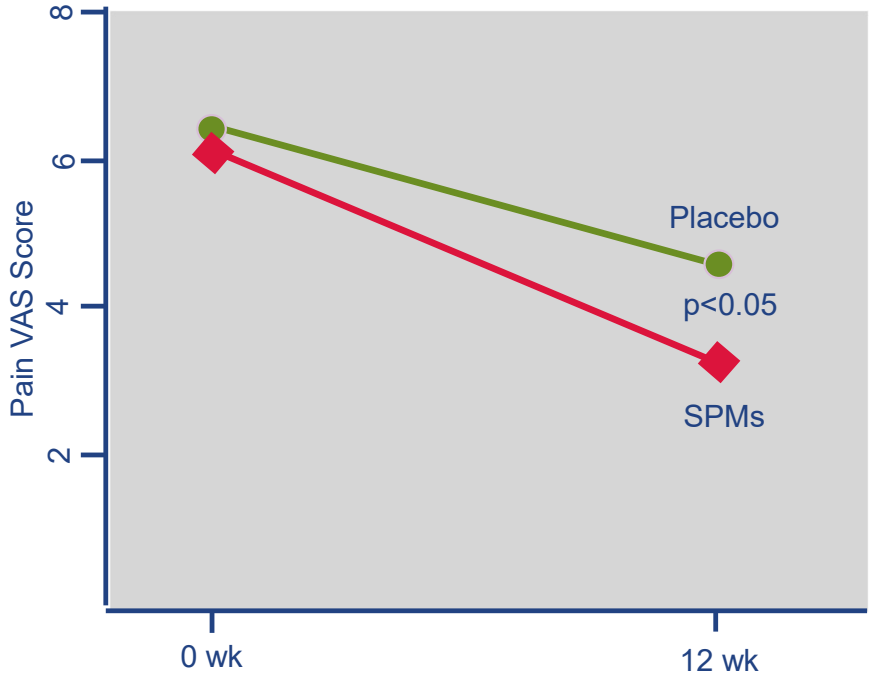
Callan N, Hanes D, Bradley R. Early evidence of efficacy for orally administered SPM-enriched marine lipid fraction on quality of life and pain in a sample of adults with chronic pain. J Transl Med. 2020 Oct 21;18(1):401. doi: 10.1186/s12967-020-02569-5.

SPMS reduce pain in Osteoarthritis



1-2 g/day or placebo
12 weeks
51 Osteoarthritis patients

SPM Improvements:
- usual activities



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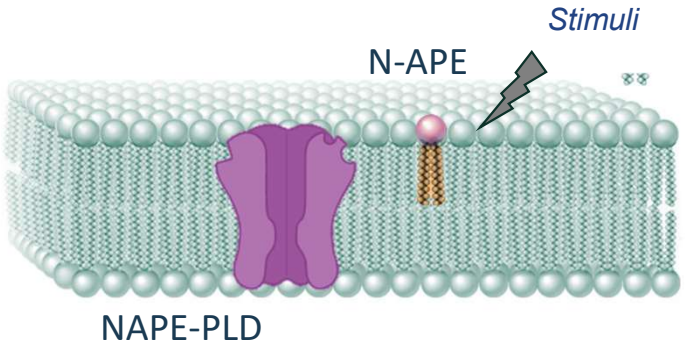
Möller I, et al. Randomized, double-blind, placebo-controlled study to evaluate the effect of treatment with an SPMs-enriched oil on chronic pain and inflammation, functionality, and quality of life in patients with symptomatic knee osteoarthritis: GAUDI study. J Transl Med. 2023 Jun 29;21(1):423. doi: 10.1186/s12967-023-04283-4

Cell membrane



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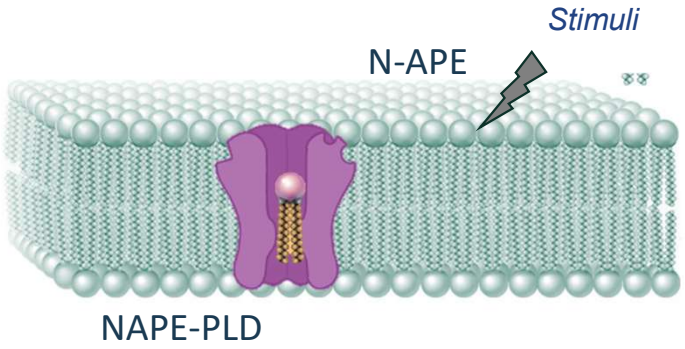
Cell membrane



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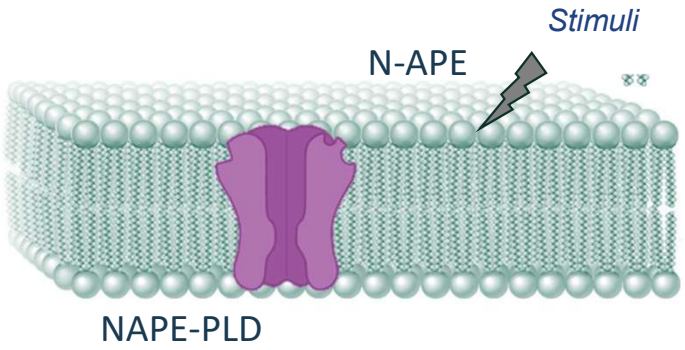
Cell membrane



PEA

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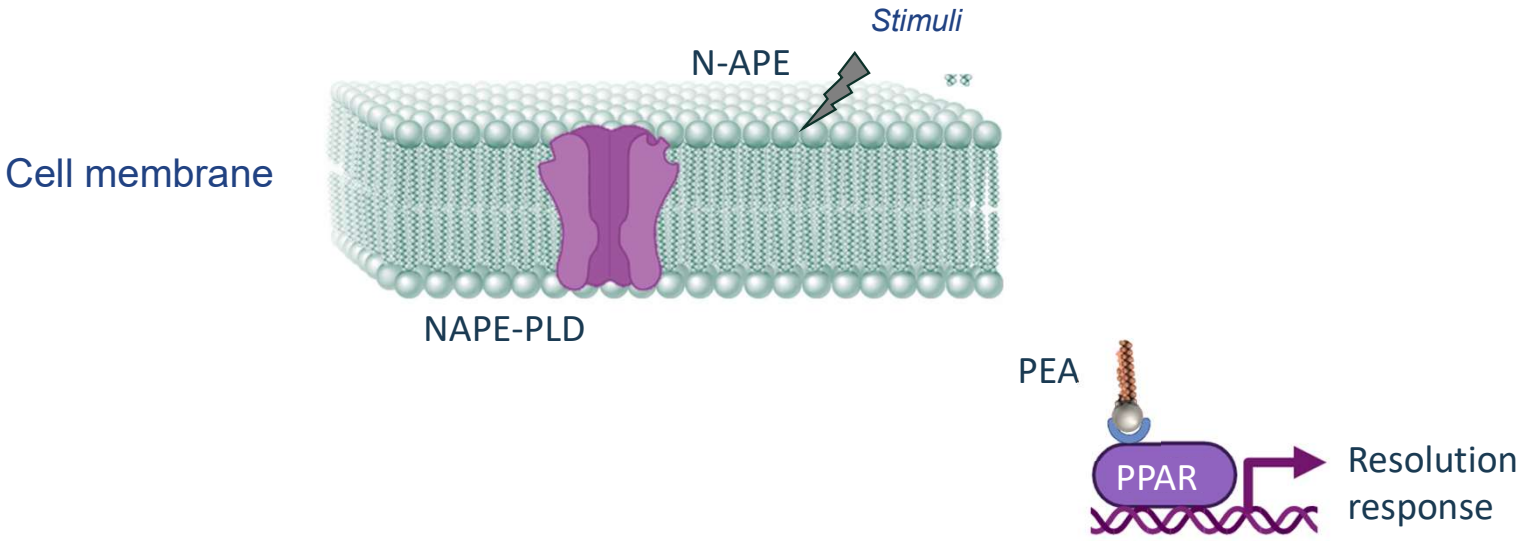

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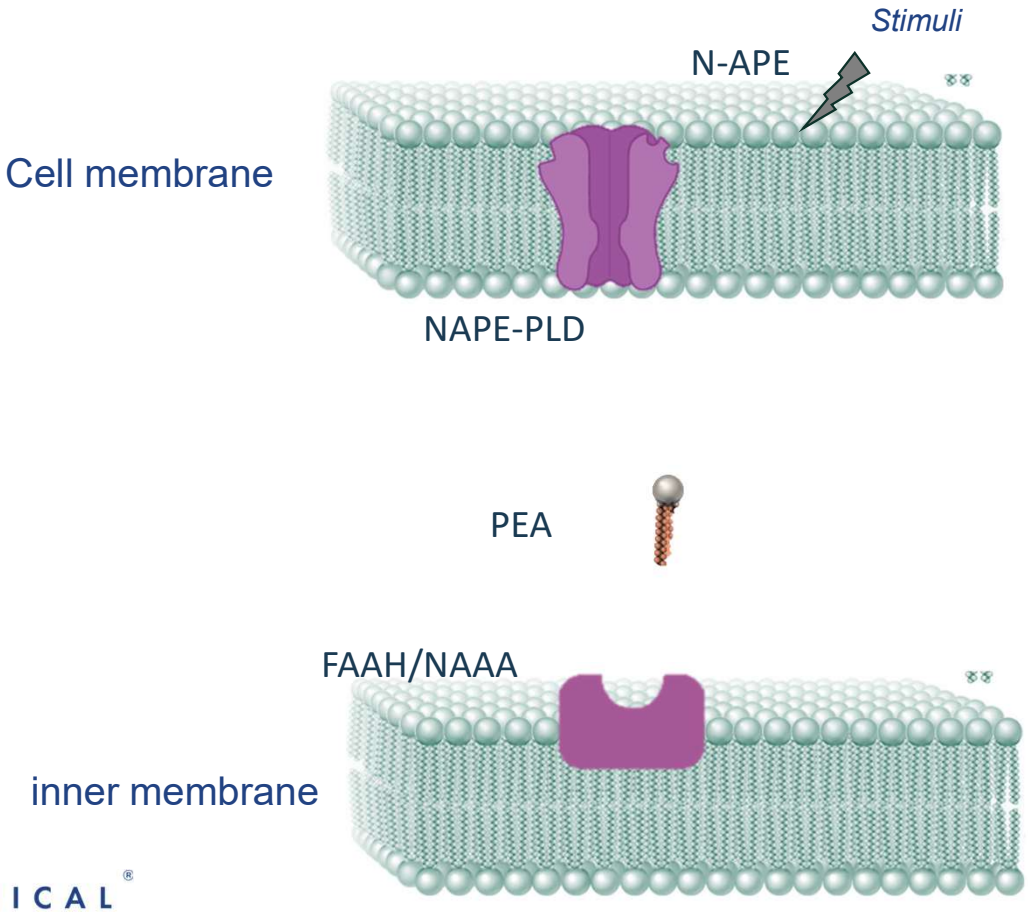

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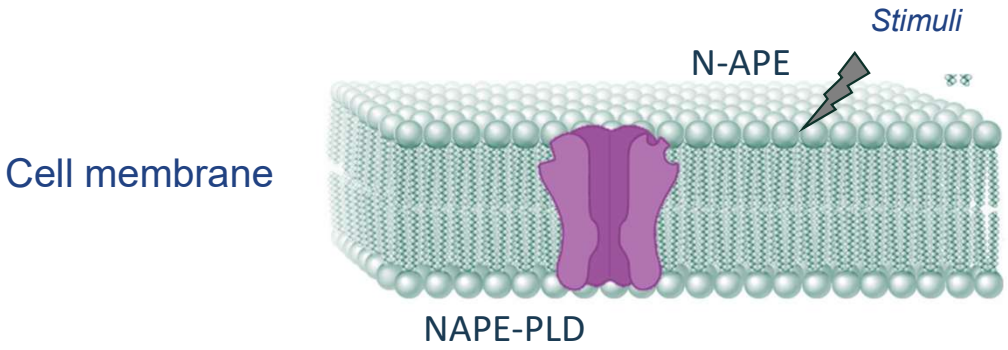
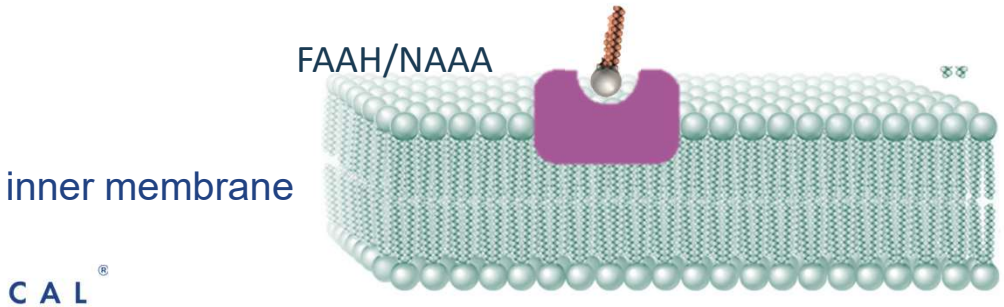


PEA



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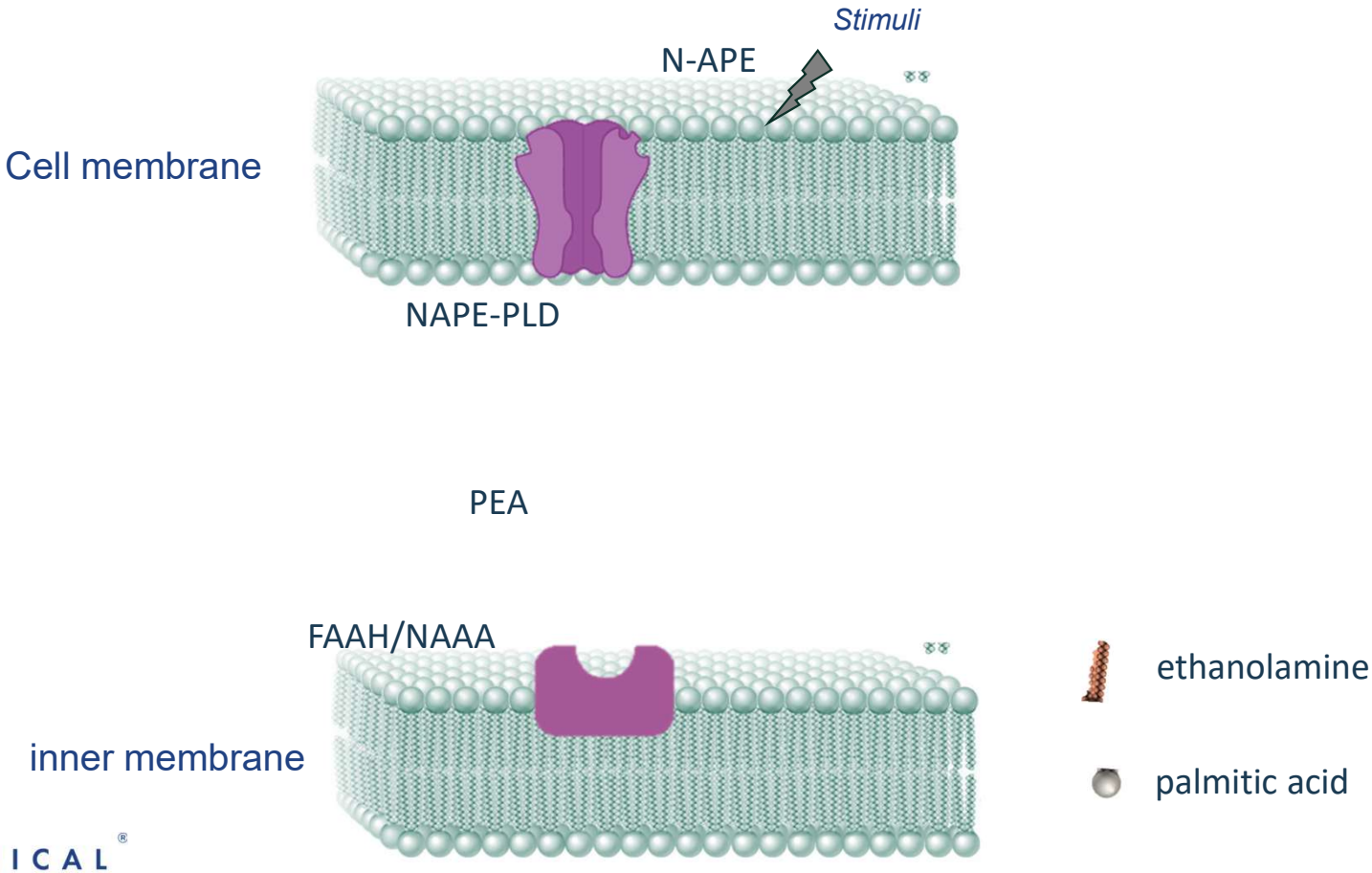

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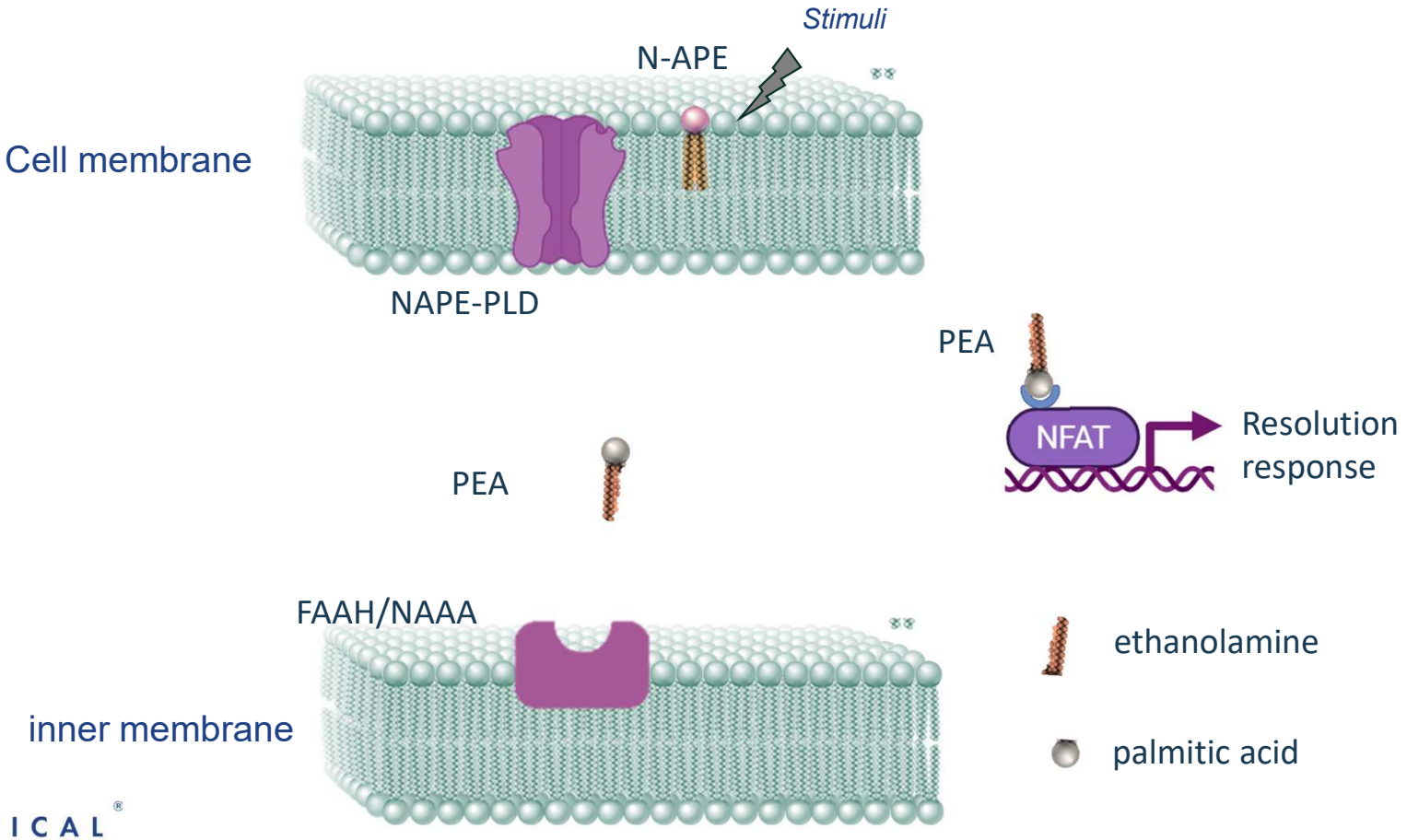

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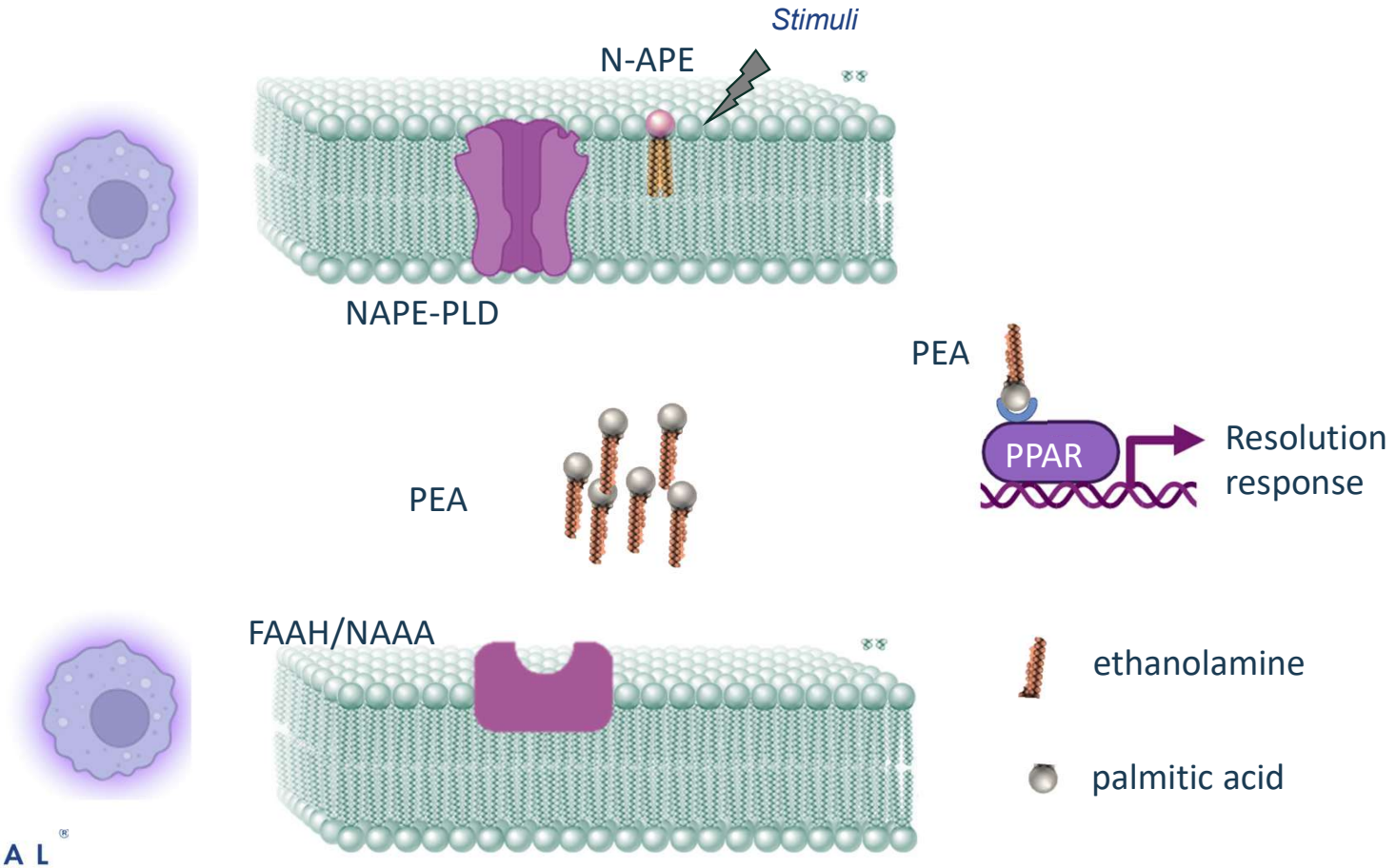

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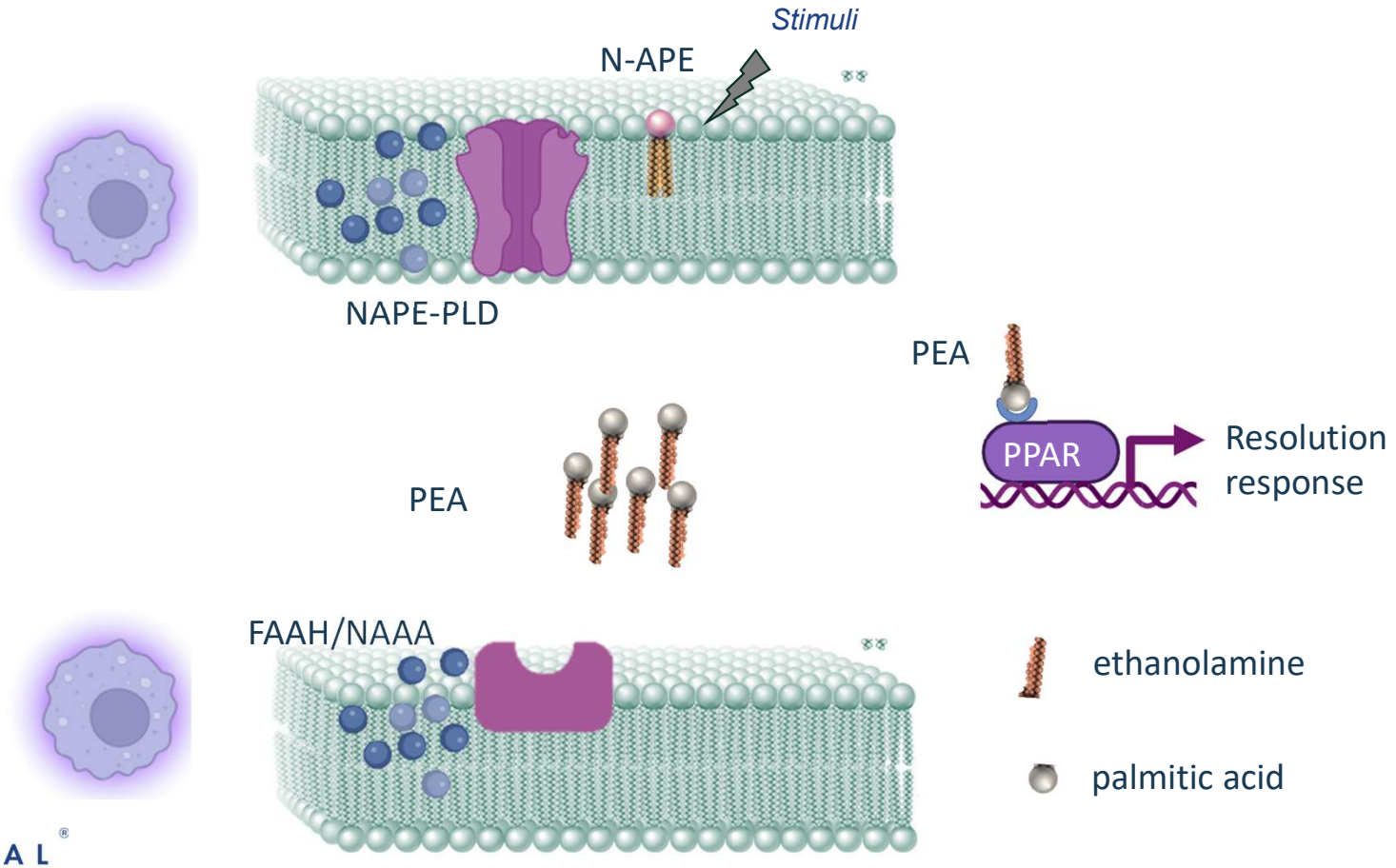

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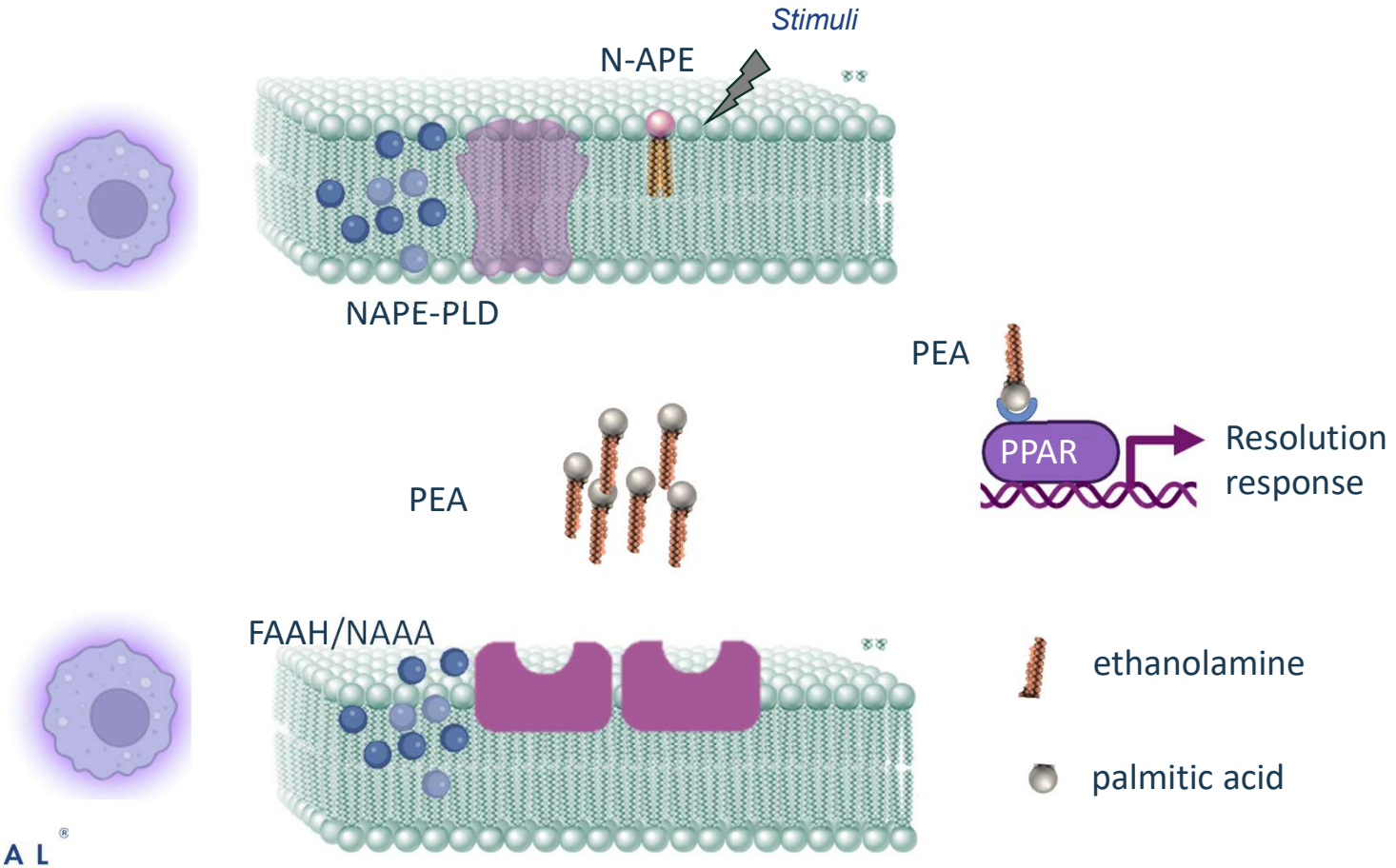

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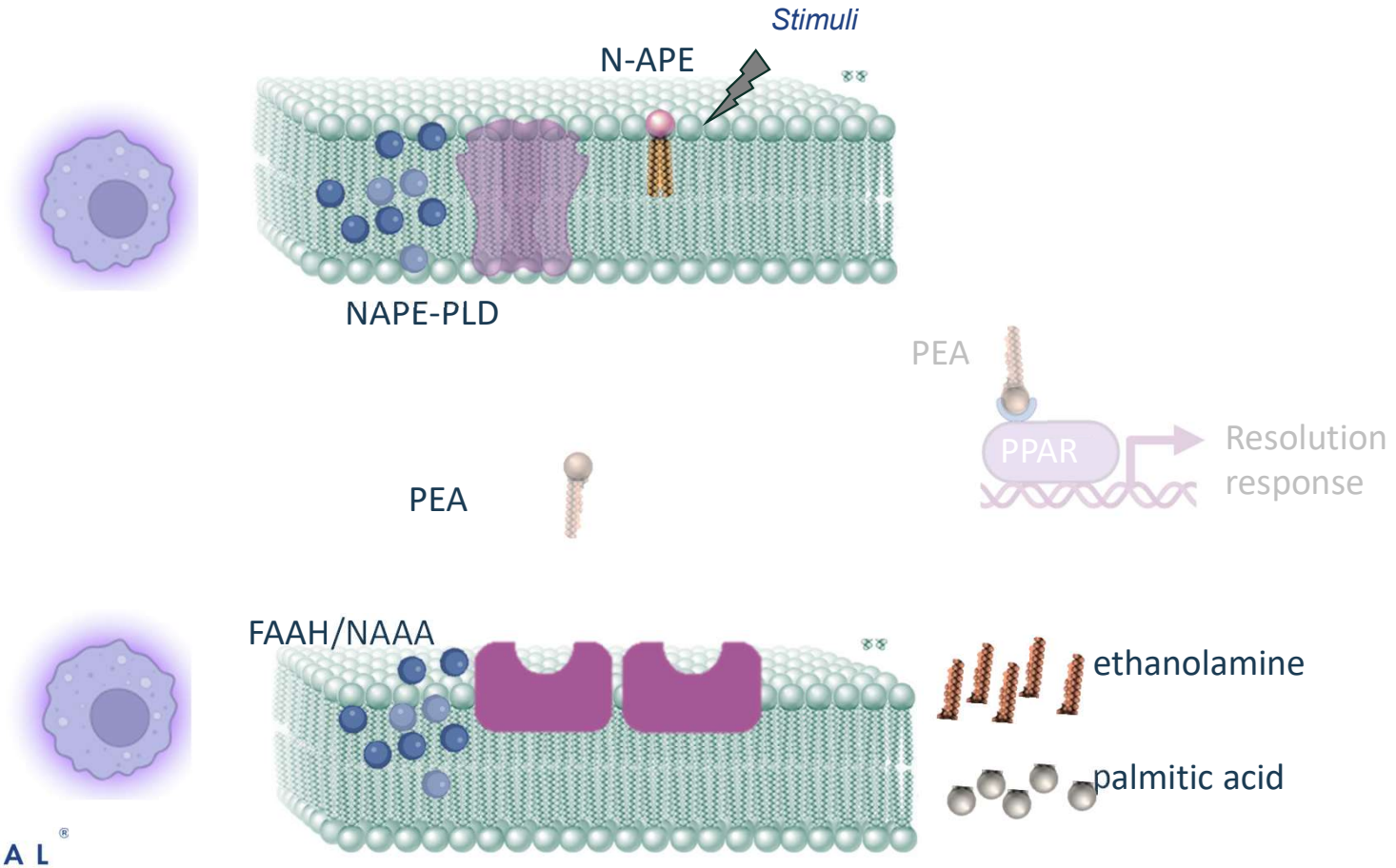

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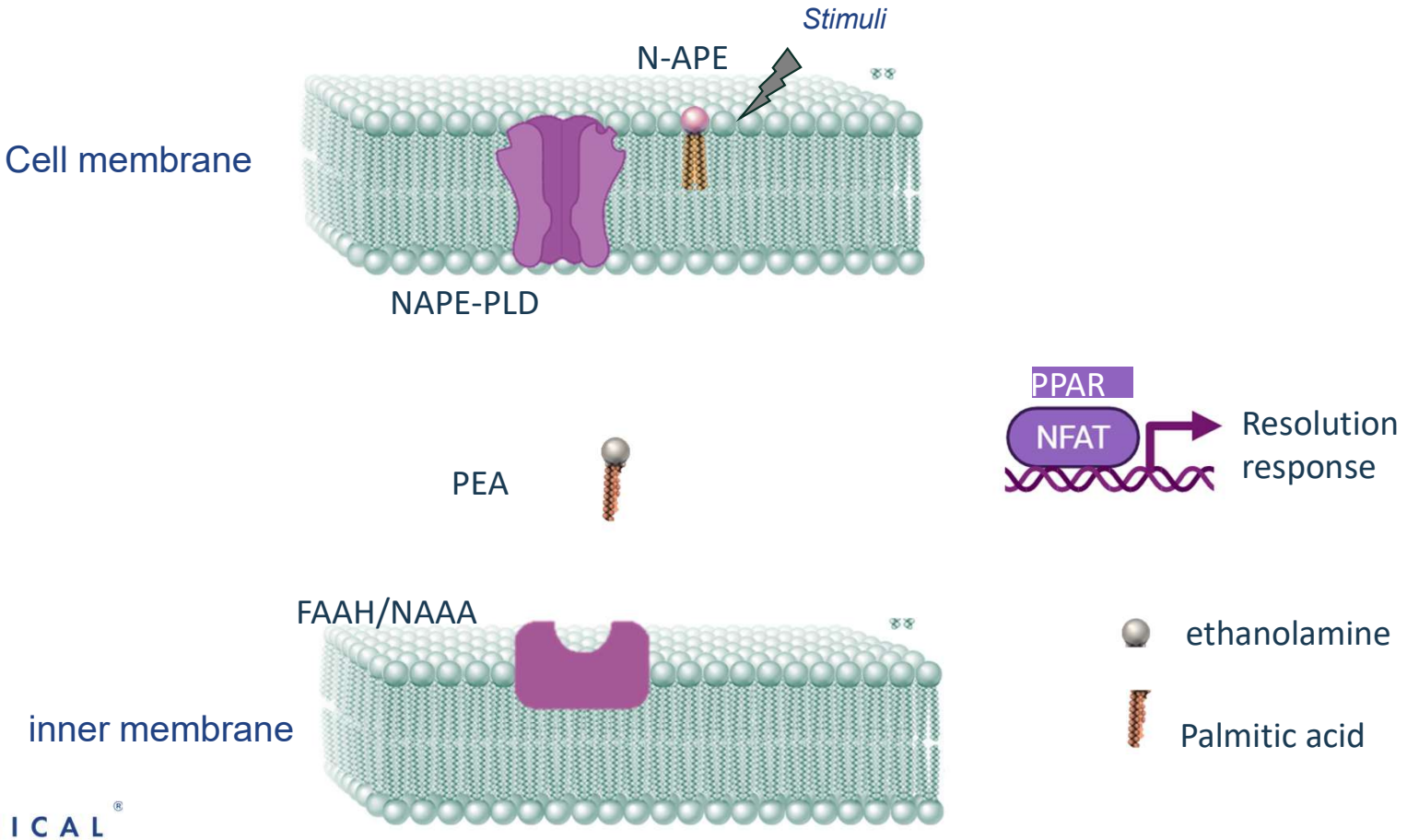

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Endogenous PEA is generally insufficient to counter chronic allostatic load as seen in chronic inflammatory disorders

Exogenous administration is a viable therapeutic strategy to top-up endogenous levels and restore bodily homeostasis

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Clayton P, Hill M, Bogoda N, Subah S, Venkatesh R. Palmitoylethanolamide: A Natural Compound for Health Management. Int J Mol Sci. 2021;22(10):5305. Published 2021 May 18. doi:10.3390/ijms22105305

Widespread efficacy of PEA

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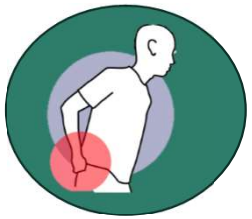
Widespread efficacy of PEA



Neuropathic Pain
(Sciatica)

- Pain ↓ 70%
- Significant pain relief after first week
- Comparable or superior to first-line neuropathic pain treatments

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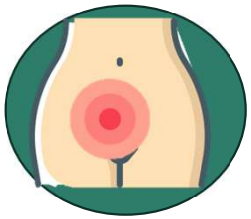
Widespread efficacy of PEA



Chronic Pelvic Pain Syndrome

- Significant ↓ in pelvic pain
- Comparable to amitriptyline
- Better safety profile and fewer withdrawals

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Widespread efficacy of PEA

Paediatric Respiratory Infections

- Over 50% ↓ in infection incidence
- Improved mucosal immunity (↑IgA)
- Safe for children

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Widespread efficacy of PEA

Migraine Prophylaxis

- ↓ headache frequency by ~50%
- ↓ duration by ~40%
- ↓ intensity by ~30%

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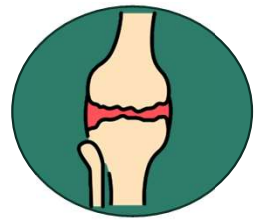
Widespread efficacy of PEA



Osteoarthritis

- Clinically meaningful pain reduction
- Rapid onset
- Comparable or superior to some pharmacologic treatments

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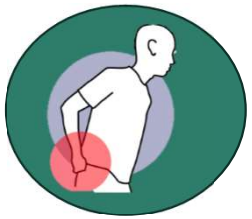
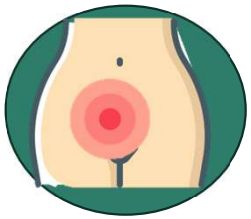
Widespread efficacy of PEA



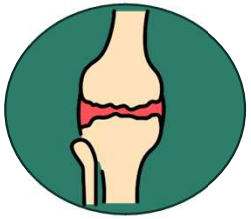
Neuropathic Pain (Sciatica)



Chronic Pelvic Pain Syndrome

Paediatric Respiratory Infections

Migraine Prophylaxis



Osteoarthritis

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Indication	Clinical Trial Dosage(s)	Reference(s)
Back pain	1200 mg/day adjunct to tapentadol	1
Carpel tunnel	300-1200 mg/day	2,3
Sciatica	300-600 mg/day	4
Diabetic neuropathy	600 mg/day	5
ALS	1200 mg/day	6
Fibromyalgia	600-1200 mg/day	7
Migraine	600 mg/day	8
Pain associated with IBS	200 mg/day	9
Endometriosis / dysmenorrhea	400 mg/day	10
Sleep	350 mg/day	11
Osteoarthritis	300-600 mg/day	12
Post-surgery (swelling and pain)	600 mg/day	13
Exercise recovery	167.5 mg/day	14

Indication	Clinical Trial Dosage(s)	Reference(s)
Depression	1200 mg/day adjunct to citalopram 40 mg	15
Parkinson's Disease	600 mg/day adjunct to levodopa	6,16
MS	600-1200 mg/day	6
Myasthenia gravis	1200 mg/day	6,17
ASD (irritability)	1200 mg/day adjunct to risperidone	18
Covid-19 (acute)	1200 mg/day	19
Long-covid (myalgia, depression, fatigue)	1200 mg/day	20
Cognitive function in young adults	700 mg/day	21
Allergic rhinitis	350 mg/day	22
Glaucoma	600 mg/day	24,25
TMJ pain	300-900 mg/day	26

References for Previous Slides

1. Passavanti MB et al. The beneficial use of ultramicronized palmitoylethanolamide as add-on therapy to Tapentadol in the treatment of low back pain: a pilot study comparing prospective and retrospective observational arms. BMC Anesthesiol. 2017;17. doi: 10.1186/s12871-017-0461-9.
2. Evangelista M et al. Ultra-micronized palmitoylethanolamide effects on sleep-wake rhythm and neuropathic pain phenotypes in patients with carpal tunnel syndrome: An open-label, randomized controlled study. CNS & Neurological Disorders-Drug Target. 2018 May 1;17(4):291-8.6. doi: 10.2174/1871527317666180420143830.
3. Conigliaro R et al. Use of palmitoylethanolamide in the entrapment neuropathy of the median in the wrist. Minerva medica. 2011 Apr 1;102(2):141-7. PMID: 21483401.
4. Keppel Hesselink JM & Kopsky DJ. Palmitoylethanolamide, a neutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome. J Pain Res. 2015 Oct 23;8:729-34. doi: 10.2147/JPR.S93106.
5. Schifilliti C et al. Micronized palmitoylethanolamide reduces the symptoms of neuropathic pain in diabetic patients. Pain Res Treat. 2014;2014:849623. doi: 10.1155/2014/849623.

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References for Previous Slides Continued

6. Landolfo E et al. Effects of Palmitoylethanolamide on Neurodegenerative Diseases: A Review from Rodents to Humans. Biomolecules. 2022 May 5;12(5):667. doi: 10.3390/biom12050667.
7. Del Giorno R et al.Palmitoylethanolamide in fibromyalgia: results from prospective and retrospective observational studies. Pain Thera. 2015 Dec;4(2):169-78. doi: 10.1007/s40122-015-0038-6.
8. Briskey D et al. Effectiveness of Palmitoylethanolamide (Levagen+) Compared to a Placebo for Reducing Pain, Duration, and Medication Use during Migraines in Otherwise Healthy Participants-A Double-Blind Randomised Controlled Study. Pharmaceuticals (Basel). 2024 Jan 23;17(2):145. doi: 10.3390/ph17020145.
9. Cremon C et al. Randomised clinical trial: the analgesic properties of dietary supplementation with palmitoylethanolamide and polydatin in irritable bowel syndrome. Aliment Pharmacol Ther. 2017 Apr;45(7):909-922. doi: 10.1111/apt.13958.
10. Stochino Loi E et al. Effect of ultramicronized-palmitoylethanolamide and co-micronized palmitoylethanolamide/polydatin on chronic pelvic pain and quality of life in endometriosis patients: An open-label pilot study. Int J Womens Health. 2019 Aug 12;11:443-449. doi: 10.2147/IJWH.S204275.

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References for Previous Slides Continued

11. Rao A et al. Palmitoylethanolamide for sleep disturbance. A double-blind, randomised, placebo-controlled interventional study. Sleep Sci Pract. 2021;5(1):12. doi: 10.1186/s41606-021-00065-3.
12. Steels E et al. A double-blind randomized placebo controlled study assessing safety, tolerability and efficacy of palmitoylethanolamide for symptoms of knee osteoarthritis. Inflammopharmacology. 2019 Jun;27(3):475-485. doi: 10.1007/s10787-019-00582-9.
13. Bacci C et al. Randomized split-mouth study on postoperative effects of palmitoylethanolamide for impacted lower third molar surgery. ISRN Surg. 2011;2011:917350. doi: 10.5402/2011/917350.
14. Mallard A et al. The Effect of Orally Dosed Levagen+™ (palmitoylethanolamide) on Exercise Recovery in Healthy Males-A Double-Blind, Randomized, Placebo-Controlled Study. Nutrients. 2020 Feb 25;12(3):596. doi: 10.3390/nu12030596.
15. Ghazizadeh-Hashemi M et al. Palmitoylethanolamide as adjunctive therapy in major depressive disorder: A double-blind, randomized and placebo-controlled trial. J Affect Disord. 2018 May;232:127-133. doi: 10.1016/j.jad.2018.02.057. Epub 2018 Feb 21. PMID: 29486338.
16. Brotini S et al. Ultra-micronized Palmitoylethanolamide: An Efficacious Adjuvant Therapy for Parkinson's Disease. CNS Neurol Disord Drug Targets. 2017;16(6):705-713. doi: 10.2174/1871527316666170321124949. PMID: 28325153

References for Previous Slides Continued

17. Onesti E et al. Short–Term Ultramicronized Palmitoylethanolamide Therapy in Patients with Myasthenia Gravis: A Pilot Study to Possible Future Implications of Treatment. CNS Neurol. Disord. Drug Targets. 2019;18:232–238. doi: 10.2174/1871527318666190131121827.
18. Khalaj M et al. Palmitoylethanolamide as adjunctive therapy for autism: Efficacy and safety results from a randomized controlled trial. J Psych Res. 2018 Aug 1;103:104-11. doi: 10.1016/j.jpsychires.2018.04.022.
19. Fessler SN et al. Palmitoylethanolamide Reduces Proinflammatory Markers in Unvaccinated Adults Recently Diagnosed with COVID-19: A Randomized Controlled Trial. J Nutr. 2022 Oct 6;152(10):2218-2226. doi: 10.1093/jn/nxac154.
20. Raciti L et al. Could Palmitoylethanolamide Be an Effective Treatment for Long-COVID-19? Hypothesis and Insights in Potential Mechanisms of Action and Clinical Applications. Innov Clin Neurosci. 2022 Jan-Mar;19(1-3):19-25. PMID: 35382075.
21. Kim N et al. Formulated Palmitoylethanolamide Supplementation Improves Parameters of Cognitive Function and BDNF Levels in Young, Healthy Adults: A Randomised Cross-Over Trial. Nutrients. 2024; 16(4):489. doi: 10.3390/nu16040489.
22. Briskey D et al. The Effect of Levagen+ (Palmitoylethanolamide) Supplementation on Symptoms of Allergic Rhinitis-A Double-Blind Placebo-Controlled Trial. Nutrients. 2023 Nov 28;15(23):4940. doi: 10.3390/nu15234940.

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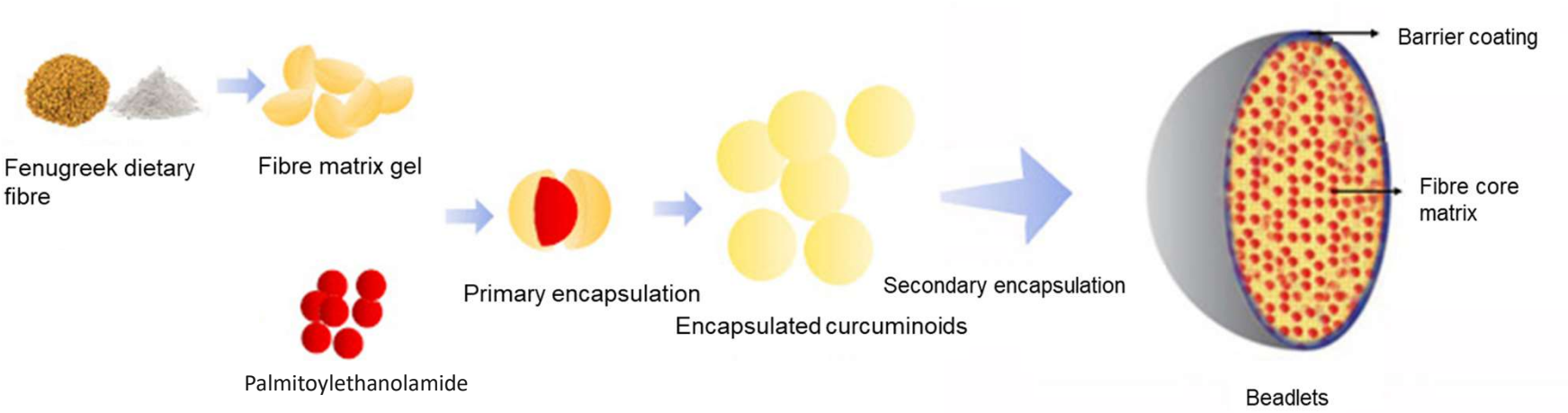
References for Previous Slides Continued

23. Cocito D et al. Short-term efficacy of ultramicronized palmitoylethanolamide in peripheral neuropathic pain. Pain Res Treat. 2014;854560. doi: 10.1155/2014/854560.
24. Gagliano C et al. Ocular hypotensive effect of oral palmitoyl-ethanolamide: a clinical trial. Invest Ophthalmol Vis Sci. 2011;52(9):6096-100. doi: 10.1167/iovs.10-7057.
25. Strobbe E et al. Effectiveness of palmitoylethanolamide on endothelial dysfunction in ocular hypertensive patients: a randomized, placebo-controlled cross-over study. Invest Ophthalmol Vis Sci. 2013;54(2):968-73. doi: 10.1167/iovs.12-10899.
26. Marini I et al. Palmitoylethanolamide versus a nonsteroidal anti-inflammatory drug in the treatment of temporomandibular joint inflammatory pain. J Orofac Pain. 2012;26(2):99-104. PMID: 22558609.

PEA + FENUMAT™ = P-Fen



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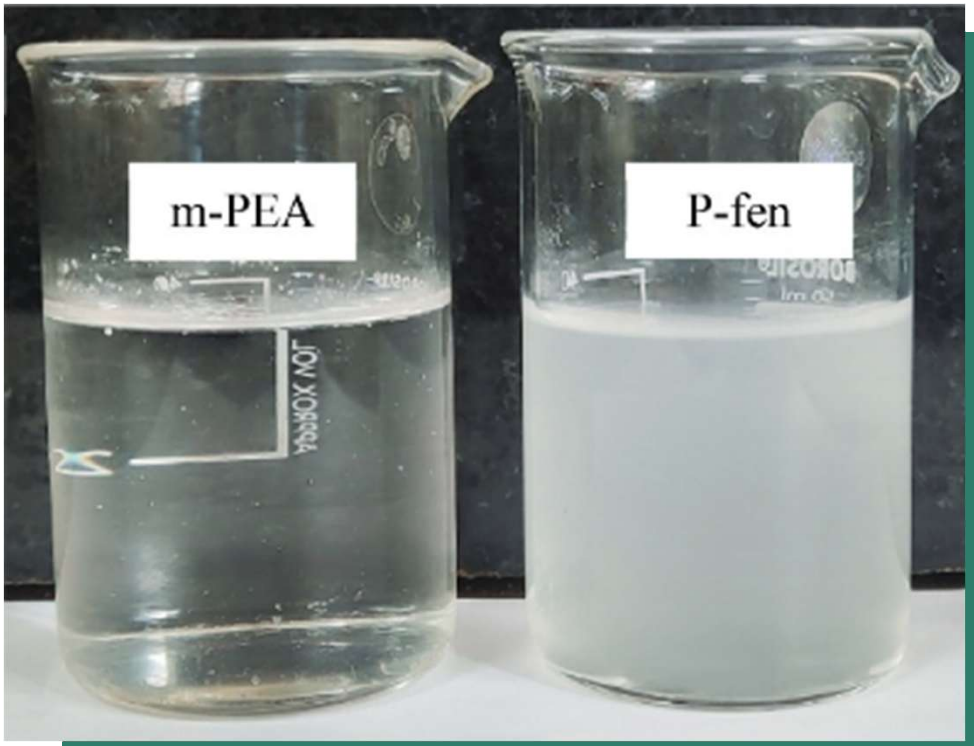

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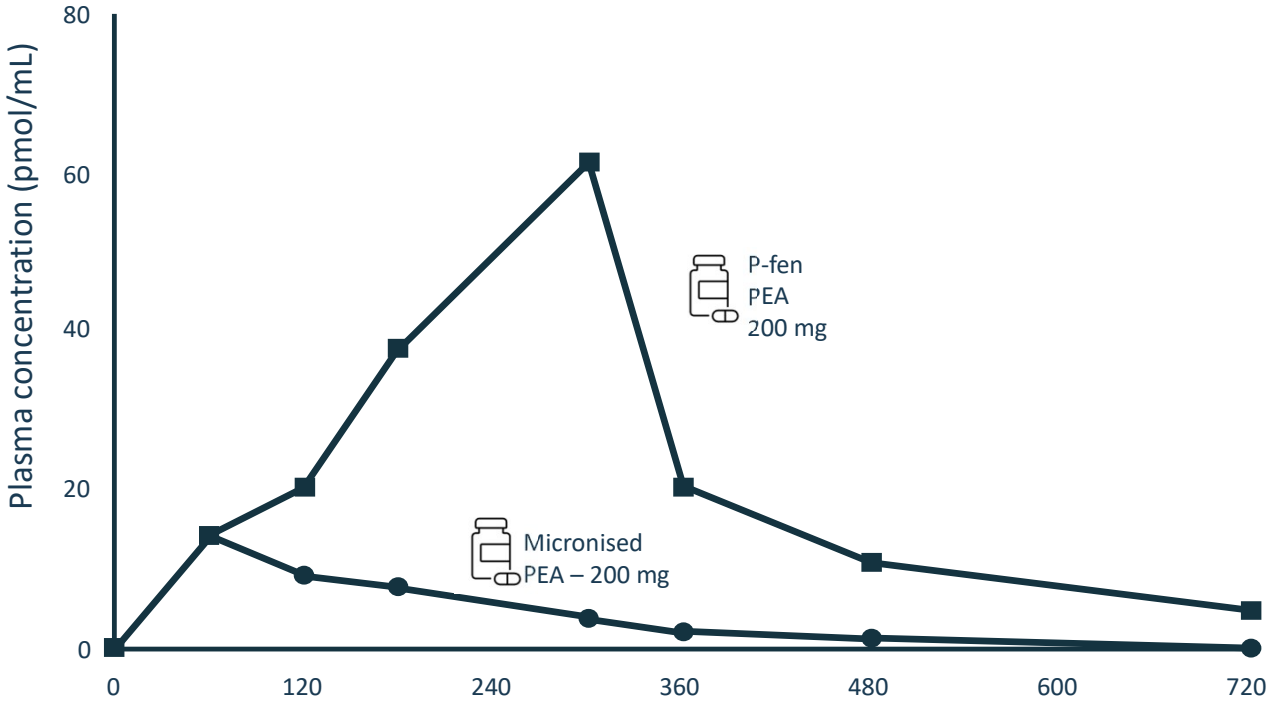
P-Fen for Improved Stability and Absorption

- **Creates a layer** around the PEA – slowing the metabolism and degradation in the GIT (slow-release)
- **Attaches to the gastric mucosal layer**, releasing into the intestinal epithelium
- **Promotes direct absorption** into circulation and lymphatic system

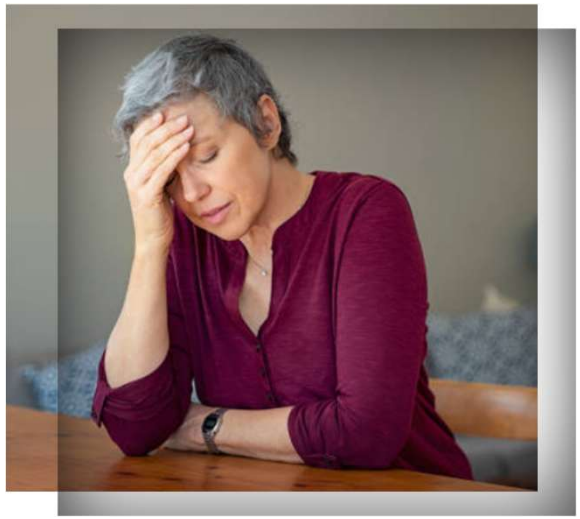
P-Fen PEA has Superior Bioavailability



Jose Louis M et al. Pharmacokinetics of a natural hybrid-hydrogel formulation of palmitoylethanolamide (PEA): randomized, single-dose, double-blinded, 2-way crossover study. Cyta-Journal of Food. 2025 Dec 31;23(1):2516484.

Case study - Migraine

- Migraines for over 50 years.
- 7 preventor medications
- Heavy pain relief medication
- Poor quality of life
- Migraine attack – 1 capsule each of SPM and PEA with CGM
- Migraine resolved – no need for preventors or pain relief



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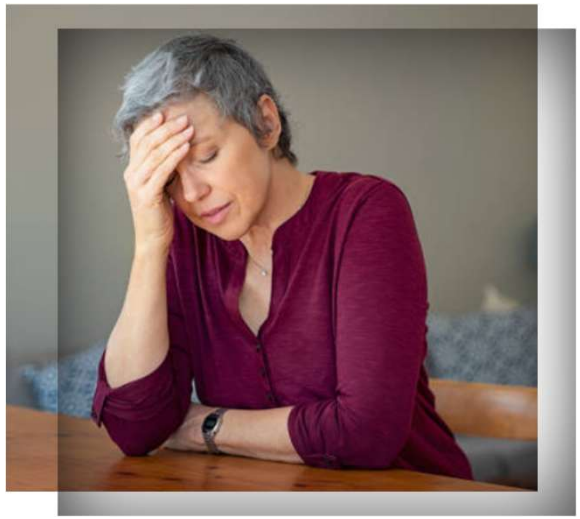
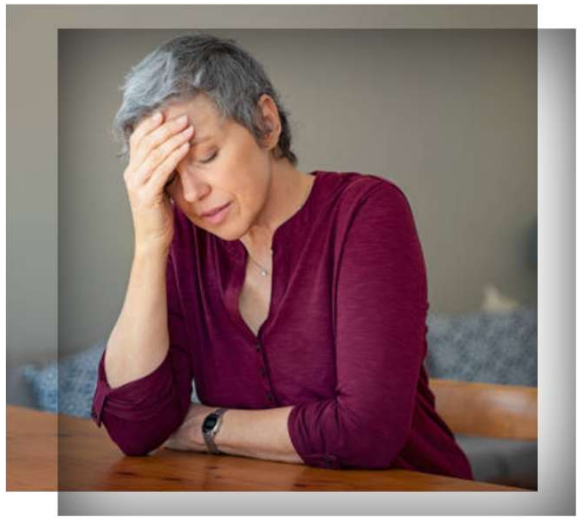


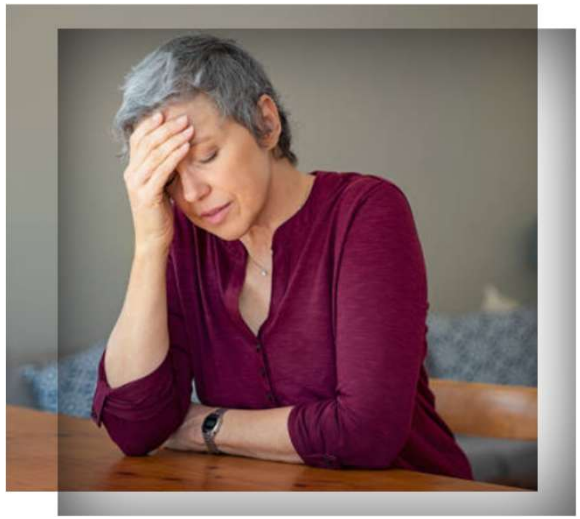
Case study - Migraine

"Now I have a bottle of PEA and SPMs with me in my bag which I take everywhere, and they have been a lifesaver to me."



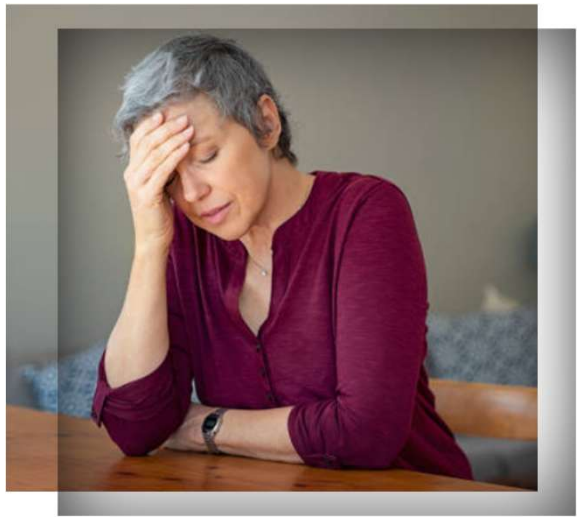
Case study - Migraine

"While I still need to take preventor medications I am so pleased to say I have reduced my reliance on pain relief medications and other migraine relief. "



Case study - Migraine

“I just can't believe that two such great supplements have had such a positive effect for me.”



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Case Study – Neurological pain

5 years of pain, tingling, electric shocks and an internal heat patch on my spine, numbness in feet and periods of fatigue
PEA with CGM – significant reduction in pain and brain fog
Pain onset - “1 cap and 20 minutes later I am pain/discomfort free”
Added 1000 mg of SPMs
Internal heat patch disappeared, and brain fog completely resolved

EAGLE CLINICAL®

Case Study – Neurological pain

5 years of pain, tingling, electric shocks and an internal heat patch on my spine, numbness in feet and periods of fatigue
PEA with CGM – significant reduction in pain and brain fog
Pain onset - “1 cap and 20 minutes later I am pain/discomfort free”
Added 1000 mg of SPMs
Internal heat patch disappeared, and brain fog completely resolved

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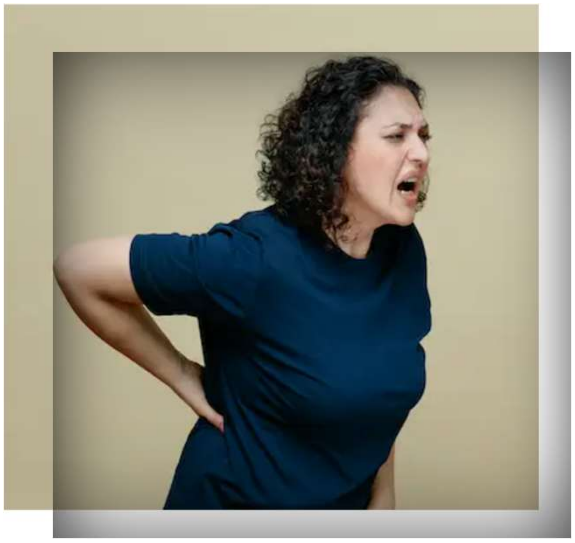
Case Study – Neurological pain



I am so grateful to have found this combo as they have changed my life...

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Case Study – Neurological pain

before I often felt like it was on the edge of tipping over into a flare…

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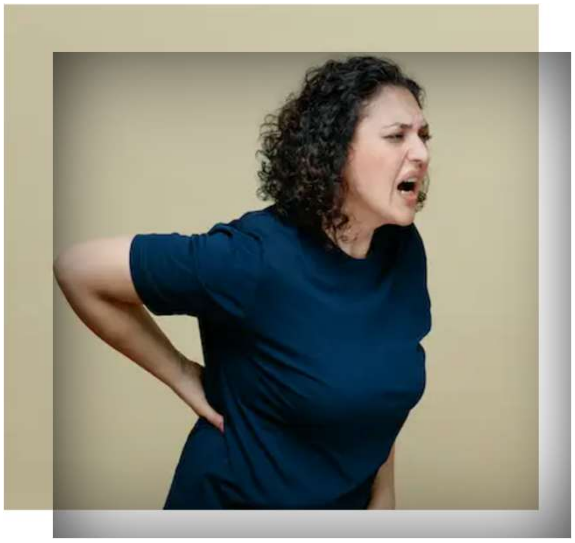
Case Study – Neurological pain



Now I feel a resilience I have not had for 5 years

EAGLE CLINICAL®


SPMs & PEA

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Conditionally essential

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Conditionally essential

Potent Clinical effects


SPMs & PEA
Conditionally essential
Potent Clinical effects
Broad applications

SPMs & PEA

Conditionally essential

Potent Clinical effects

Broad applications

Rapid acting

SPMs & PEA

Conditionally essential

Potent Clinical effects

Broad applications

Rapid acting

Safe

Thank you

You are invited to our educational event

The Incretin Revolution: What Every Natural Healthcare Practitioner Needs to Know

Presented by Nathan Rose

Tuesday, 23rd June 2026
College of Naturopathic Medicine
25 Percy Circus, London WC1X 9EU

Thursday, 25th June 2026
The Pendulum Hotel and Conference Centre,
Weston Building, Sackville Street,
Manchester M1 3BB