Uncharted territories: treatments for the resolution of inflammation

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COI and Recent Support

- **2021-2025** NIMH R01MH123451 “Latino Ancestry Genomic Psychiatry Cohort (AAGPC)” (PI: Pato, Site PI: Rapaport) $90,000 subcontract annual direct
- **2021-2023** NCI R21CA263453-01 “Massage for Prostate Cancer-Related Fatigue” (PI: Rapaport) $150,000 annual direct
- **2020-2021** NIDA UG3DA48502 **“**Non-Invasive Vagal Nerve Stimulation in Patients with Opioid Use Disorders” (PI: Bremner, Co-I: Rapaport) $76,865 annual direct
- **2015-2020** NCCIH UG3 AT008857-01 “Omega-3 Fatty Acids for MDD with High Inflammation: A Personalized Approach” (PI: Rapaport) $1,029,613 annual direct
- **2015-2021** NIH R01 “African American Genomic Psychiatry Cohort” (PI: Pato, Site PI: Rapaport), $130,000 annual direct
- **2015-2019** NCCIH 1R01AT009169-01 “Mechanism of Action for n-3 PUFA Antidepressant Properties” (PI: Rasenick, Site PI: Rapaport) $250,000 annual direct
- **2014-2019** NIMH 1R25MH101079-01:”Emory Psychiatry Clinical Scientist Training Program (CSTP)” (PI: Ressler/Miller, Mentor: Rapaport), $968,142
- **2012-2015** NIMH HHS-NIH-MH-2010-024 “Double-Blind, Proof-of-Concept (POC) Trial of Low Field Magnetic Stimulation (LFMS),” (PI: Fava, Site PI: Rapaport), Total costs $358,045.
- **2012-2017** NIMH 1K23MH098014-01: “A Potential State and Relapse Predictive Marker in Schizophrenia (PI: B Miller, Mentor: Rapaport), Total costs $170,600
- **2013-2018** NIMH MH100023-01: “Silvio O. Conte Center for Oxytocin and Social Cognition,” (PI: L Young, Co-I: Rapaport), Total costs $1,161,874

The Goals of the Presentation

- Discuss the importance of personalized approaches to clinical trial design- using the treatment of inflammation as an example
- Describe the challenges of employing immune measures as biomarkers
- Suggest the presence of an entirely new class of targets for drug development- using our work with N-3 fatty acids as an example
- Describe potential design and study characteristics

Inflammation is a necessary process but uncontrolled inflammation becomes pathological

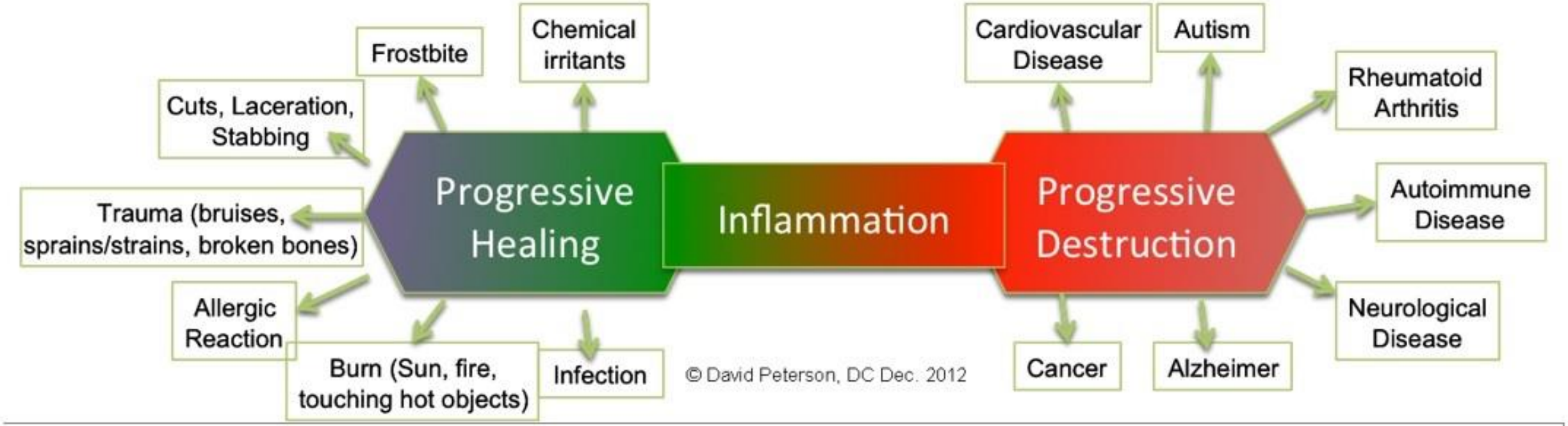
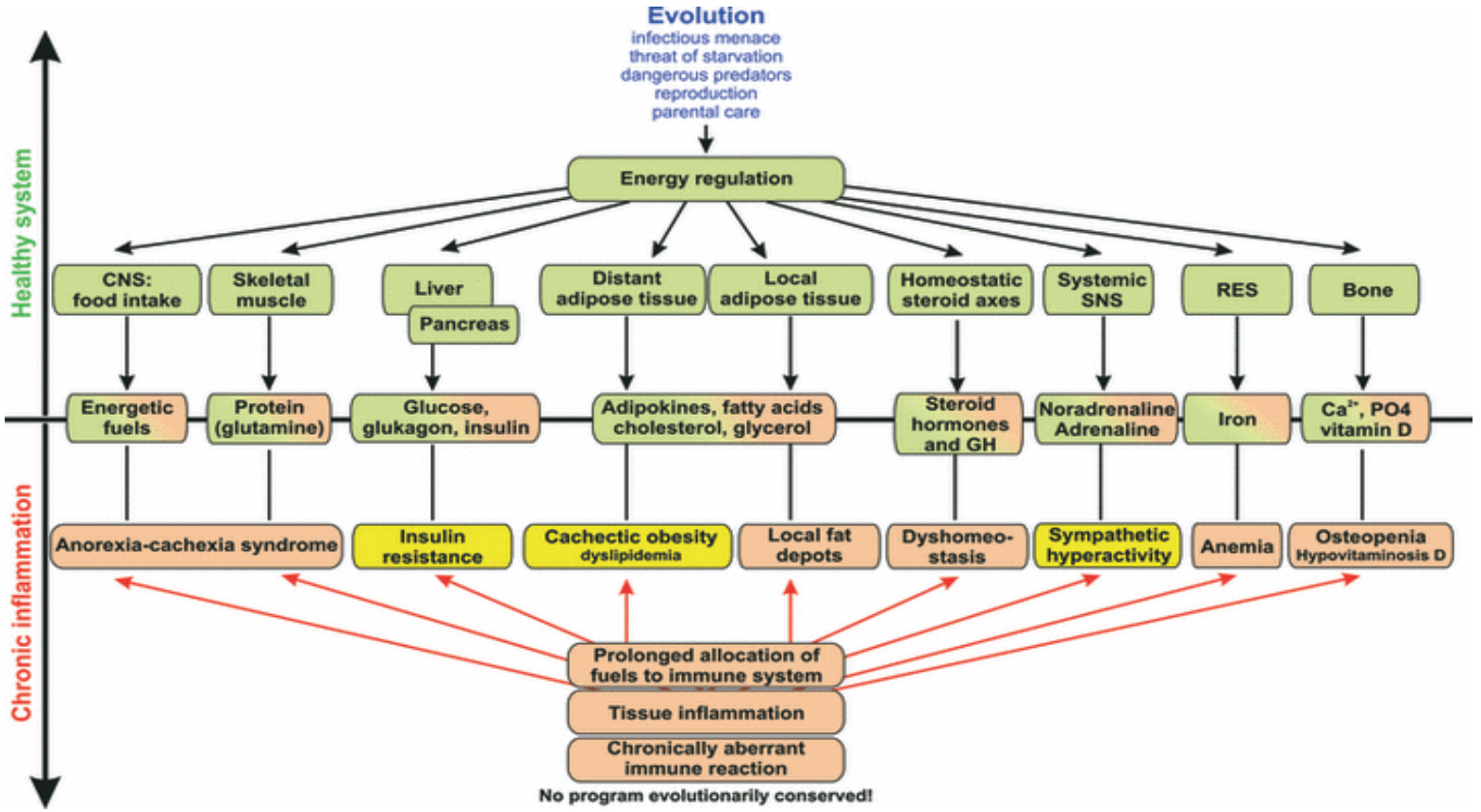


Figure 1: A brilliant example of how inflammation can lead to both health and disease

Immune system control of energy regulation and neuroendocrine function in acute inflammation and chronic inflammatory diseases



Journal of Internal Medicine
Volume 267, Issue 6, pages 543-560, 28 JAN 2010 DOI: 10.1111/j.1365-2796.2010.02218.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2010.02218.x/full#f4

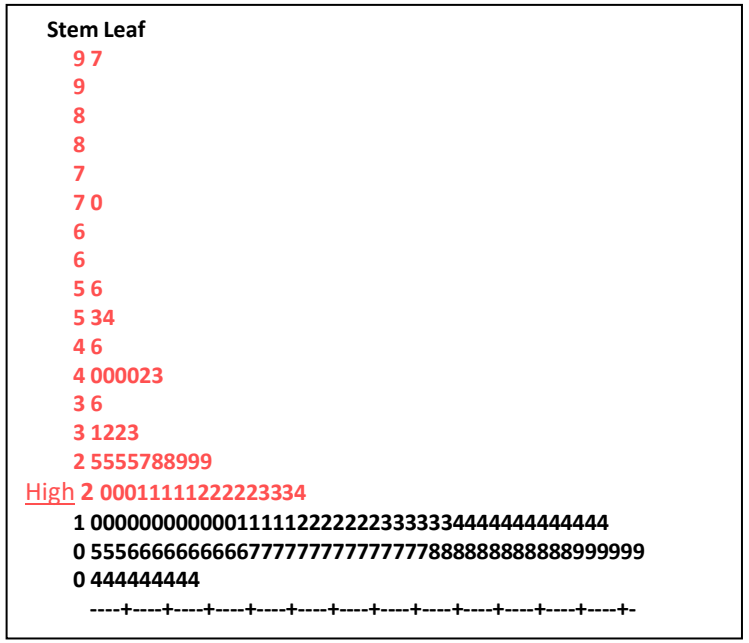
EPA vs. DHA vs. Placebo

- 177 subjects with MDD: Mean Ham-D= 19
- Randomized 1 gm/day EPA-enriched, 1gm/day DHA-enriched or placebo for 8 weeks
- Overall MMRM analysis of change in HAM-D-17 scores over 8 weeks of treatment, we found no significant difference among EPA-enriched treatment (mean change = -10.34), DHA-enriched treatment (mean change = -9.26), and placebo (mean change = -9.49).
- Standardized treatment effect sizes indicated very modest superiority of EPA-enriched treatment over placebo or the DHA-enriched formulation (effect sizes of -0.179 and -0.228, respectively)
- A negligible treatment difference between DHA-enriched treatment and placebo (effect size of +0.049).

Source: Mischoulon et al submitted

Inflammatory status:

The cut-points for 'high' markers of inflammation were based on stem-and-leaf plots (except for established level of >3.0 for hs-CRP), which we then applied to our evaluable sample with all 5 biomarkers (N=155). **(MH Rapaport et al Mol Psych 2015)**



Inflammatory Marker	N	Definition Of High Inflammation	N (%) Defined As High
hs-CRP (mg/l) [a]	174	> 3.00	41 (23.6%)
IL-6 (pg/ml) [b]	174	> 1.92	44 (25.3%)
IL-1ra (pg/ml) [b]	167	> 500	51 (30.5%)
Leptin (mg/l) [b]			
Females	103	≥ 250	31 (30.1%)
Males	72	≥ 70	19 (26.4%)
Adiponectin (mg/l) [b, c]			
Females	103	< 80	39 (37.9%)
Males	72	< 60	37 (51.4%)

a. Based on conventional definition of high inflammation.
b. Based on stem-and-leaf plot for all subjects with each marker present at baseline.
c. Low values of adiponectin indicate high levels of inflammation.

Spearman Correlations among Baseline Values of Body Mass Index (BMI) and 5 Inflammatory Markers – 91 Females in Analysis Sample.

Spearman Correlation Coefficient
Prob > |r| under H0: Rho=0
Number of Observations

	BMI	hs-CRP	IL-6	IL-1ra	Leptin	Adiponectin
BMI	1.00000 86	0.68560 <.0001 86	0.63470 <.0001 86	0.46617 <.0001 86	0.85515 <.0001 86	-0.40851 <.0001 86
hs-CRP	0.68560 <.0001 86	1.00000 91	0.55066 <.0001 91	0.39137 0.0001 91	0.58916 <.0001 91	-0.39581 0.0001 91
IL-6	0.63470 <.0001 86	0.55066 <.0001 91	1.00000 91	0.48898 <.0001 91	0.58486 <.0001 91	-0.39677 <.0001 91
IL-1ra	0.46617 <.0001 86	0.39137 0.0001 91	0.48898 <.0001 91	1.00000 91	0.42518 <.0001 91	-0.34709 0.0007 91
Leptin	0.85515 <.0001 86	0.58916 <.0001 91	0.58486 <.0001 91	0.42518 <.0001 91	1.00000 91	-0.20971 0.0460 91
Adiponectin	0.40851 <.0001 86	-0.39581 0.0001 91	-0.39677 <.0001 91	-0.34709 0.0007 91	-0.20971 0.0460 91	1.00000 91

MH Rapaport et al Mol Psych 2015

Spearman Correlations among Baseline Values of Body Mass Index (BMI) and 5 Inflammatory Markers – 64 Males in Analysis Sample.

Spearman Correlation Coefficient
Prob > |r| under H0: Rho=0
Number of Observations

	BMI	hs-CRP	IL-6	IL-1ra	Leptin	Adiponectin
BMI	1.00000 58	0.33563 .0100 58	0.34566 .0079 58	-0.11618 .3851 58	0.61149 <.0001 58	-0.28106 .0326 58
hs-CRP	0.33563 .0100 58	1.00000 64	0.56160 <.0001 64	0.30074 0.0157 64	0.47310 <.0001 64	-0.01579 0.9014 64
IL-6	0.34566 .0079 58	0.56160 <.0001 64	1.00000 64	0.33473 .0069 64	0.42335 .0005 64	-0.11957 .3467 64
IL-1ra	-0.11618 .3851 58	0.30074 0.0157 64	0.33473 .0069 64	1.00000 64	0.15513 .2209 64	0.00350 0.9781 64
Leptin	0.61149 <.0001 58	0.47310 <.0001 64	0.42335.0 005 64	0.15513 .2209 64	1.00000 64	-0.19001 0.1326 64
Adiponectin	-0.28106 .0326 58	-0.01579 0.9014 64	-0.11957 .3467 64	0.00350 0.9781 64	-0.19001 0.1326 64	1.00000 64

MH Rapaport et al Mol Psych 2015

The Number of high markers of inflammation by BMI Category within Gender

MH Rapaport et al Mol Psych 2015

	Females (N = 86)			Males (N = 58)		
	Underweight or Normal Weight	Overweight	Obese	Underweight or Normal Weight	Overweight	Obese
N	39	18	29	12	27	19
%	45.3	20.9	33.7	20.7	46.6	32.8
Number of High Inflammatory Biomarkers						
4 or 5	0 (0.0)	0 (0.0)	14 (48.3)	0 (0.0)	2 (7.4)	4 (21.0)
2 or 3	3 (7.7)	5 (27.8)	11 (37.9)	3 (25.0)	4 (14.8)	10 (52.6)
1	12 (30.8)	8 (44.4)	2 (6.9)	6 (50.0)	14 (51.8)	3 (15.8)
None	24 (61.5)	5 (27.8)	2 (6.9)	3 (25.0)	7 (25.9)	2 (10.5)
Any High Inflammatory Biomarker	15 (38.5)	13 (72.2)	27 (93.1)	9 (75.0)	20 (74.1)	17 (89.5)

Summary

- **25/29 (86%) of obese women with MDD have 2 or more high markers of inflammation.**
- **14/19 (74%) of obese men with MDD have 2 or more high markers of inflammation.**

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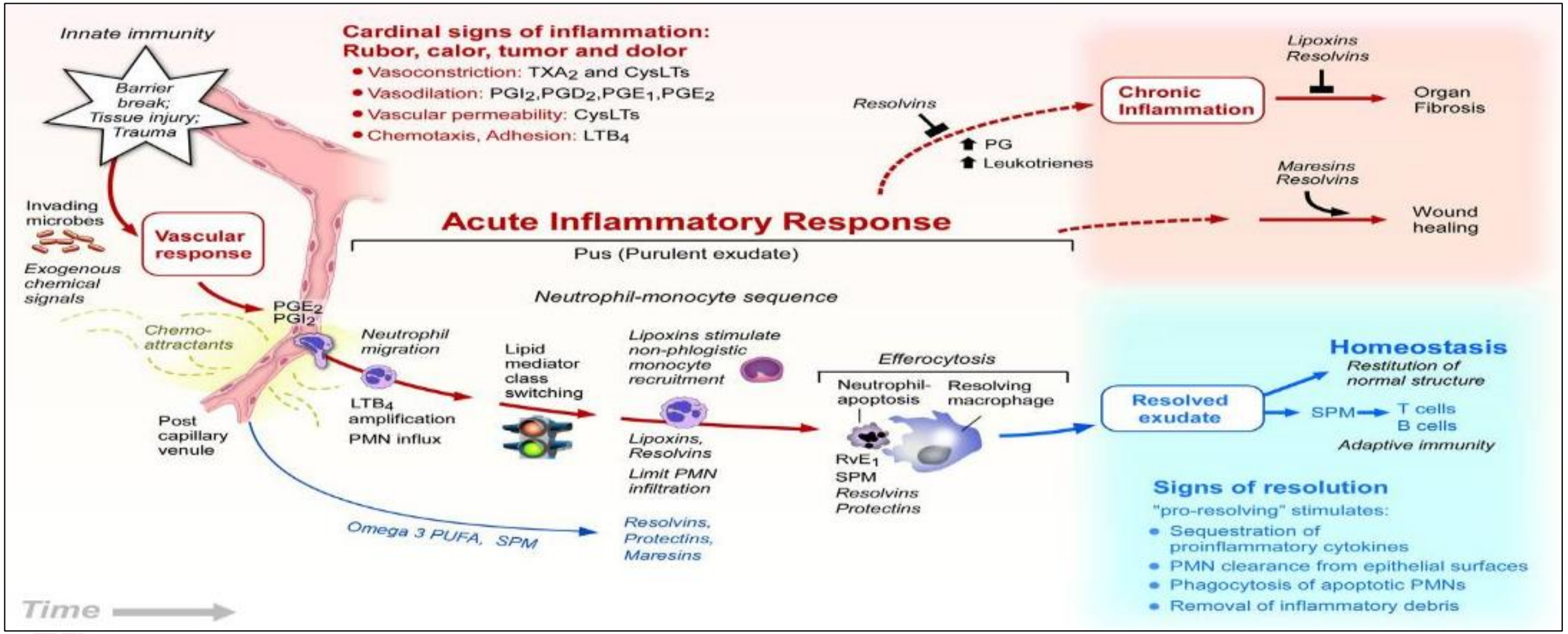
OMEGA-3 FATTY ACIDS FOR MDD WITH HIGH INFLAMMATION: A PERSONALIZED APPROACH: AN UG3

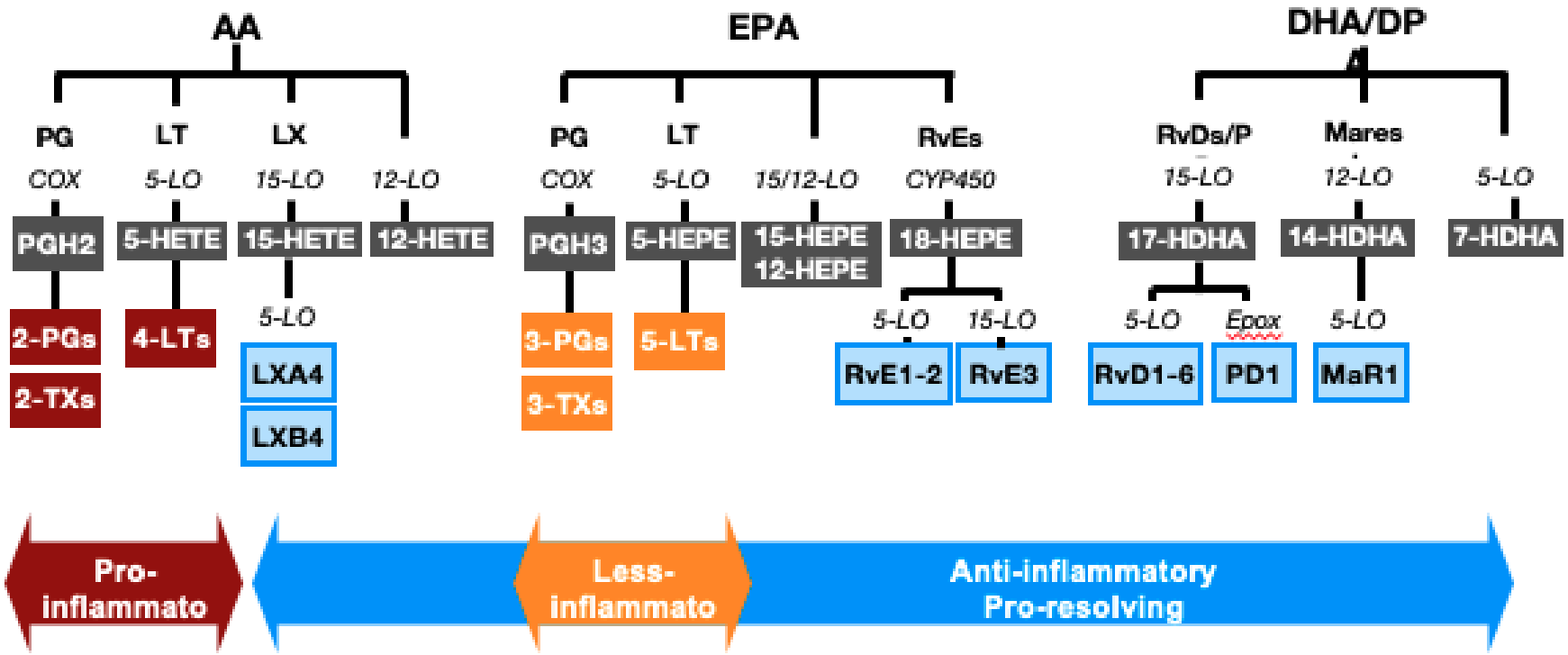
Mark H. Rapaport, MD, Maurizio Fava, MD, David Mischoulon, MD, PhD, Boadie Dunlop, MD, Jennifer Felger, PhD, Becky Kinkead, PhD, Andrew Miller, MD, Jeffrey Rakofsky, MD, Pamela Schettler, PhD, Thomas Ziegler, MD, Andrew Nierenberg, MD, Jonathan Alpert, PhD, Christina Dording, MD, Stephania Fava, PhD

Funding: NCCIH UG3AT008857

Lipid mediators in the acute inflammatory response, resolution and other outcomes



SPM biosynthetic pathways



IVC Resolvin E1, E2, and E3 all have antidepressant activity in the LPS-induced mouse model of depression

Deyama et al Int J Neuropscyhophamacol. 2017:20; 571-584;
Deyama et al j.jphs.2018.09.006

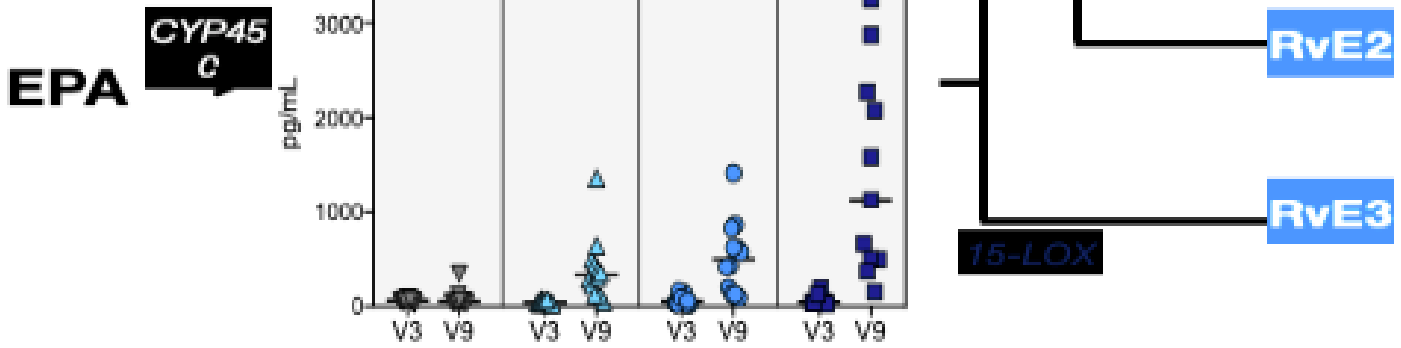
Correlation of % Change in IDS-C30 with % Change Plasma hs-CRP (n=48 Completers)

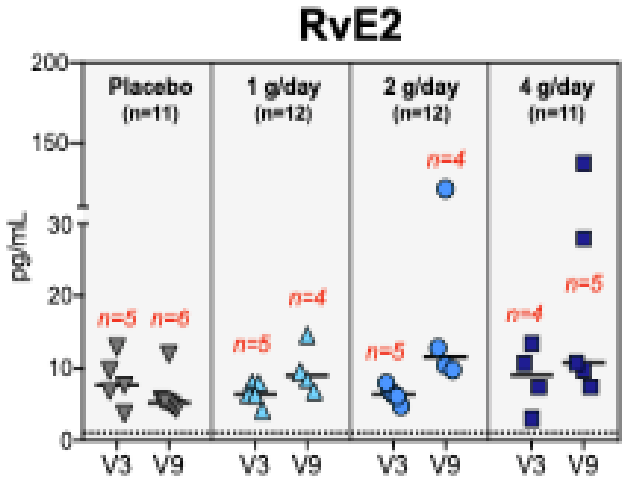
Percent Change from Baseline	Spearman Rank-Order Correlation with Percent Change in IDS-C30 at Treatment Week 12 (Correlation, p=value, and n)			
	1g/day	2g/day	4g/day	Placebo
Plasma hs-CRP	-0.129 p=0.694 13	-0.091 p=0.790 n=11	0.753 p=0.003 13	0.164 p=0.652 10

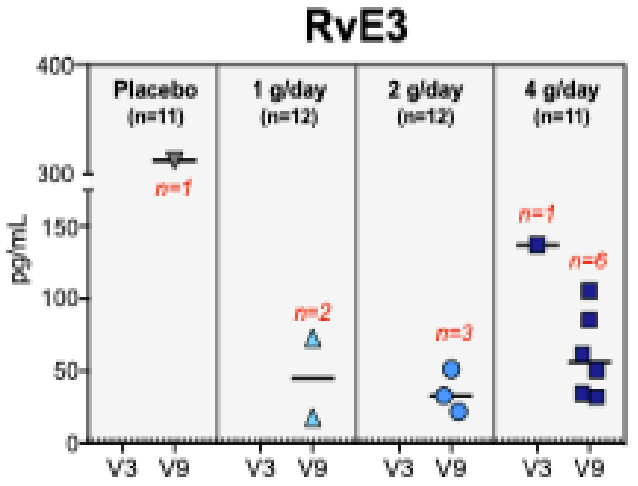
IDS-C30 Response (≥50% Reduction in Total Score) (n=48 Completers)

Tx Week	1g/day n/n (%)	2g/day n/n (%)	4g/day n/n (%)	Placebo n/n (%)	EPA Dose vs. Placebo	Risk Ratio: EPA Dose vs. Placebo	Odds Ratio: EPA Dose vs. Placebo
Week 8	3/13 (23.1)	4/11 (36.4)	8/13 (61.5)	5/10 (50.0)	1g vs. Pla 2g vs. Pla 4g vs. Pla	0.461 0.727 1.231	0.300 0.571 1.600
Week 12	5/14 (35.7)	4/11 (36.4)	9/13 (69.2)	4/10 (40.0)	1g vs. Pla 2g vs. Pla 4g vs. Pla	0.893 0.909 1.731	0.833 0.857 3.375
Both Tx Week 8 and 12	3/13 (23.1) Includes all 3 responders at Wk 8	4/11 (36.4) Includes all 4 responders at Wk 8	6/13 (46.2) Includes 6 of 8 responders at Wk 8	2/10 (20.0) Includes 2 of 5 responders at Wk 8	1g vs. Pla 2g vs. Pla 4g vs. Pla	1.154 1.818 2.308	1.200 2.286 3.429

EPA-derived RvEs

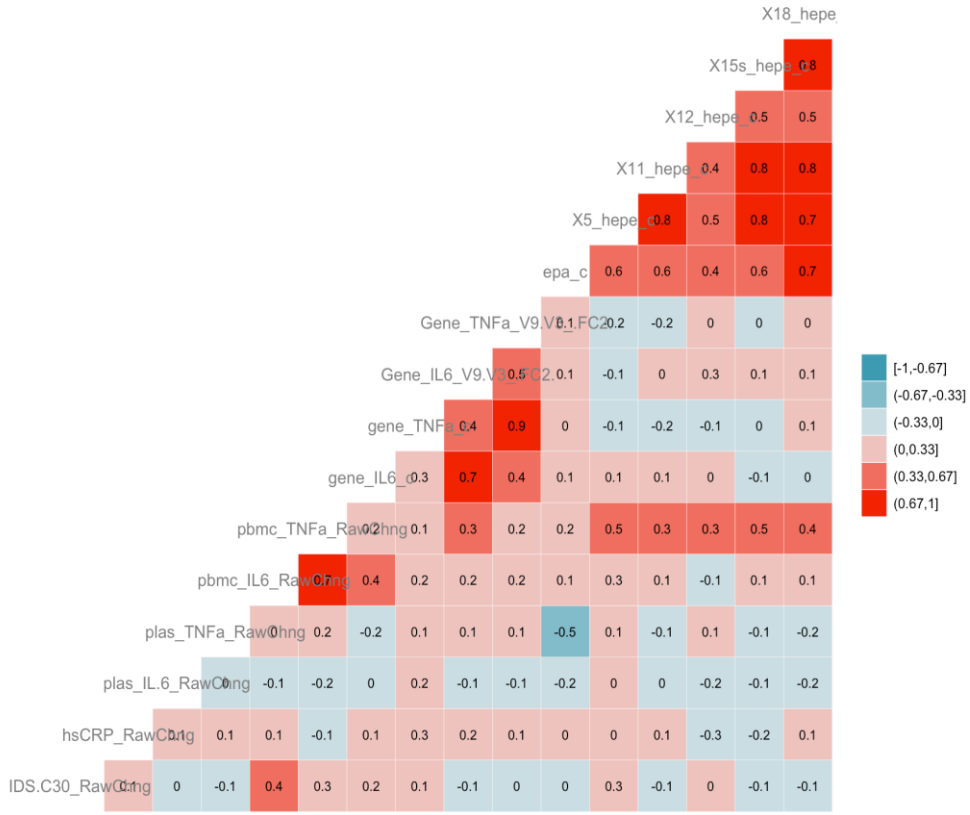




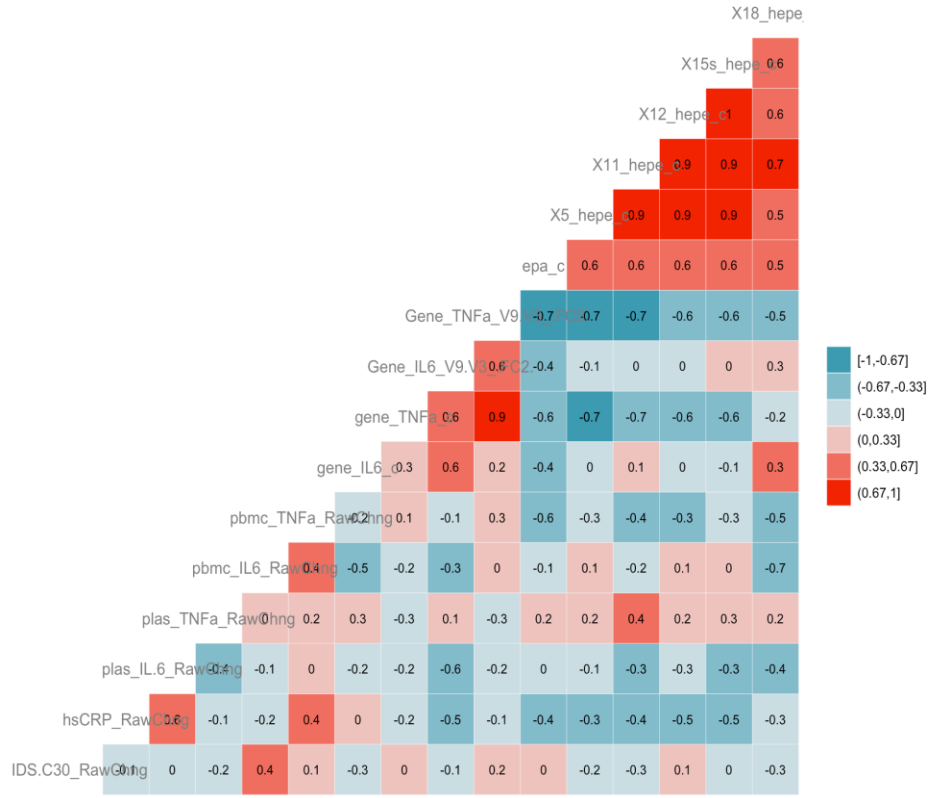


EPA/EPA-SPMs

Females



Males



Implications of our findings for future trial design

- Patient heterogeneity is a major problem- consider enrichment strategies based on sex, a stable and elevated marker of inflammation
- Be careful in determining your biomarkers of interest: how are you defining ”high”, serum vs plasma measures vs mitogen stimulated? Are there sex differences? What assays? Which technologies? How are you handling undetectable levels?
- Are you employing the right statistical approach? Do your data of interest truly meet parametric assumptions? What type of outcome makes the most sense- for example, a composite outcome of inflammation vs. a single variable

Implications of our findings for future trial design II

- Is the study design appropriate:
  - parallel sequential designs, non-inferiority designs, experimental therapeutic designs, diseases modification designs
  - Will the length of the study truly answer the key questions
  - Has there been adequate dose-response work done

- We need to tailor the inclusion and exclusion criteria to better answer the true question at hand:
  - For a TRD augmentation trial, we believe in taking all comers who have been stable on their therapies (medications, psychotherapies or other for 6 weeks) but still meet the immune and the clinical criteria
  - How do you appropriately take into account possible absorption issues?
  - How do you take into account diet- we use a food processor log to estimate the baseline intake of N-3s

Look beyond the street light to find the Keys

There are many potential targets that enhance the resolution of inflammation. They may be considerably safer than our current approach with biologicals.