Nutraceuticals: Challenges and Opportunities

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Conflicts of interest relevant to this presentation

- Previous funding from NCCAM to investigate the mechanism of action of Swedish massage therapy in normal volunteers
- Previous funding from NCCAM and NIMH to investigate the efficacy of St. John's Wort in minor depressive disorder
- Previous funding from NIMH investigating N-3 fatty acid therapy on immune function and the treatment of major depressive disorder
- Current funding from NCCIH to study the effects of massage on Cancer-related fatigue
- Current funding from NIMH for the GPC collection and RAPID trials
- Current funding from NCCIH investigating the impact of N-3 fatty acids on inflammation in obese, inflamed subjects with MDD

Collaborators

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YOU GOTTA KNOW THE TERRITORY!

Professor Henry Hill, “The Music Man”

It is important to remember

- Many of the medications commonly prescribed today were initially purified from plant extracts or fungi

What percent of pharmaceuticals manufactured in China are “traditional” natural products?

10%
27%
36%
56%
72%

- The current answer is 36%; Thirty-six percent of all pharmaceuticals manufactured in China are derived from natural products identified by traditional medicine practitioners.

“Lost in Translation 1”

Many of the natural products on the US market are part of the other healing traditions:

TRADITONAL:

Chinese Medicine

Tibetan Medicine

Hmong Medicine

Mongolian Medicine

Cunanderos/Yerberos

Ayurveda Medicine

Differences between ‘traditional medicine’ and allopathic medicine

TRADITIONAL	ALLOPATHIC
Holistic Approach	Treatment focuses on a specific target
Individualized treatment based on “pattern differences”	Standardized Treatment
Practice based on traditions, clinical experience and individual observations	Practice and use of medications based on FDA guidelines, practice guidelines
Subjective Outcome Assessment of individuals	Standardized and validated target specific outcomes

Some of the challenges

“SQUARE PEG in a ROUND HOLE PHENOMENA”

Natural products are:

- Used for very different constellations of signs and symptoms in native cultures
- We in the US are employing them to treat our definition of disorders

What you see may be what you get

- Unsubstantiated Claims of Benefit

- Minimal GPC/GM Standards

  2/3 of St. John's wort compounds contained no St. John's wort

  Rate of deterioration of compounds are not known or standardized.

  The dosage and formulation may vary between batches

“Natural may not be safe”

- Products may not be natural
- There may be many unforeseen interactions

  - Pharmacokinetic

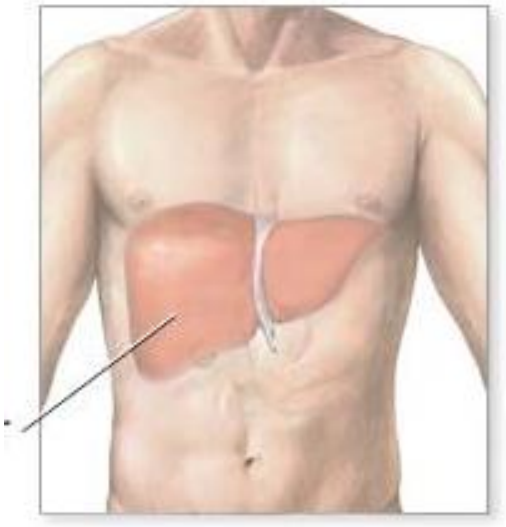
  - Pharmacodynamic

Kava (Piper Methysticum)

- Anxiolytic, anticonvulsant, and muscle relaxant (kavapyrones)
- More than 12 studies, mostly RCTs
- Similar efficacy to venlafaxine, buspirone, opipramol (sigma antagonist)
- Effective for mild anxiety, not for panic attacks (Sarris et al, 2011)
- Antidepressant effect? (Sarris et al, 2009)

Kava: Adverse Effects

- 78 cases of severe kava-related liver toxicity
- 36 cases of hepatitis; cirrhosis
- 11 cases of liver failure requiring transplant
- 4 deaths



Effects of herbs on drug-metabolizing enzymes and transporters

Herbs	*In Vitro*	Animal	Clinical	
Goldenseal (Hydrastis canadensis)	↓CYP2C9, 2C19, 3A4 and 2D6		↓CYPD26 and 3A4/5	
Green Tea (Camellia sinensis)	↓CYP2C9, 2D6, and 3A4		↓CYP3A4	
Milk Thistle (Sylibum marianum)	↓CYP3A4, 2C9, 2E1, 2D6, 2C19, 1A2 and 2A6, P-gp, UGT1A1	↓CYP3A, 2C9 and P-gp	↑CYP3A4 and P-gp; ↓CYP2C9 and P-gp	
St. John's Wort (Hypericum perforatum)	↑CYP3A4, 2C9 and P-gp		↑CYP3A4, OAT and P-gp	

Hu M, Fan L, Hong-Hao Z and Tomlinson B. *Theranostics meets traditional Chinese medicine: rational prediction of drug-herb interactions*, Expert Rev. Mol Diagn 12(8), 815-830 (2012)

Effect of genetic polymorphisms on herb-drug interactions

Herbs	Drugs	Effect of genetic polymorphisms on herb-drug interaction	Effect of genetic polymorphisms on the activity/protein/mRNA levels of the drug-metabolizing enzymes and drug transporters	Ref
St. John's wort	Gliclazide	Treatment of St. John's wort significantly increased the apparent clearance of gliclazide which was independent of CYP2C9 genotype	Reduced with the variant allele	[166]
	Mephenytoin	St. John's wort treatment significantly increased phenytoin clearance in CYP2C19 extensive metabolizers but not in PMs (*2,*3)	Reduced with the variant allele	[167]
	Nifedipine	After administration of St. John's wort, the AUC $_{0-\infty}$ of nifedipine and dehydronifedipine decreased by 42.4 and 20.2% in PXR H1/H2; 47.9 and 33.0% in H2/H2; whereas for the H1/H1 the AUC $_{0-\infty}$ of nifedipine decreased 29.0%, but the AUC $_{0-\infty}$ of dehydronifedipine increased by 106.7%.	Reduced basal transcriptional activity, but stronger induced transcriptional activity on CYP3A4 with H1/H1 compared with H1/H2 and H2/H2	[168]
	Omeprazole	St. John's wort decreased the plasma concentrations of omeprazole in a CYP2C19 genotype-dependent manner	Reduced with the variant allele	[169]

AUC – Area under the curve; CVP- Cytochrome P450; INR – International normalized ratio; PK – Pharmacokinetic; PM – poor metabolizer; PXR – Pregnane X receptor

Hu M, Fan L, Hong-Hao Z and Tomlinson B. *Theranostics meets traditional Chinese medicine: rational prediction of drug-herb interactions*. Expert Rev. Mol Diagn 12(98) 815-830 (2012)

The Opportunities

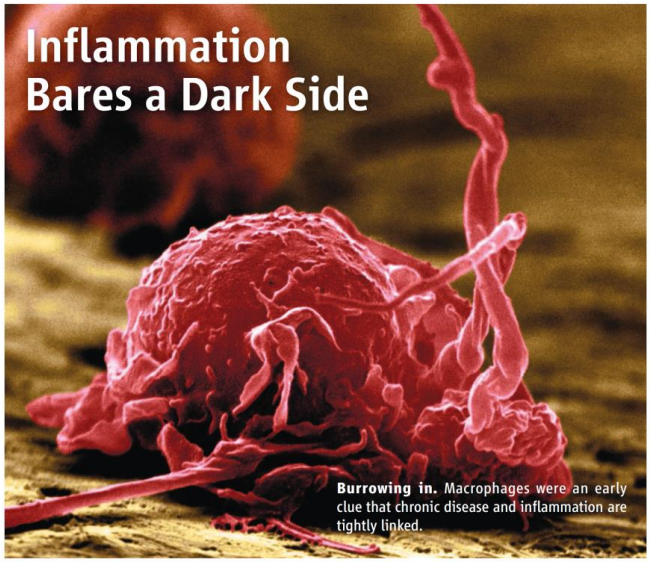
The Example of Major Depressive Disorder

CANMAT recommendations for natural products

Intervention	Indication	Recommendation	Evidence	Monotherapy or Adjunctive Therapy
St. John's wort	Mild to moderate MDD Moderate to severe MDD	First Line Second Line	Level 1 Level 2	Monotherapy Adjunctive
Omega-3	Mild to moderate MDD Moderate to severe MDD	Second line Second line	Level 1 Level 2	Monotherapy or adjunctive Adjunctive
SAM-e	Mild to moderate MDD Moderate to severe MDD	Second line Second line	Level 1 Level 2	Adjunctive Adjunctive
Acetyl-L-carnitine *Crocus sativus* (saffron)	Mild to moderate MDD Mild to moderate MDD	Third line Third line	Level 2 Level 2	Monotherapy Monotherapy or adjunctive
DHEA Folate	Mild to moderate MDD Mild to moderate MDD	Third Line Third Line	Level 2 Level 2	Monotherapy Adjunctive
Lavandula (Lavender) Inosital	Mild to moderate MDD Mild to moderate MDD	Third Line Not recommended	Level 3 Level 2	Adjunctive
Tryptophan Rhodiala rosea (roseroot)	Mild to moderate MDD Mild to moderate MDD	Not recommended Not recommended	Level 2 Insufficient evidence	

DHEA – dehydroepiandrosterone; MDD – major depressive disorder; SAM-e – S-adenosyl-L-methionine

Ravindran AV, Balneaves LG, Faulkner G et al. *Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 5. Complementary and Alternative Medicine Treatments,* La Revue Canadienne de Psychiatrie 61(9) 581



Inflammation: A Common Mechanism of Disease - Insight of the Decade (*Science*, 2010)

Demographic Characteristics Subjects with All 5 Biomarkers at Baseline			EPA-Enriched (N = 52)	DHA-Enriched (N = 51)	Placebo (N = 52)	Significance		
Age [a]		Mean (sd) [Range] (N)	46.7 (11.9) [21 - 73] (50)	45.9(14.2) [23 - 70] (49)	45.6(12.0) [22 - 69] (49)	F 0.11	df 2, 145	P 0.900
Study Site	**Cedars-Sinai** **MGH**	N (%) N (%)	32 (61.5) 20 (38.5)	30 (58.8) 21 (41.2)	32 (61.5) 20 (38.5)	x^2 0.11	df 2	P 0.948
Gender	**Female** **Male**	N (%) N (%)	33 (63.5) 19 (36.5)	28 (54.9) 23 (45.1)	30 (57.7) 22 (42.3)	x^2 0.81	df 2	P 0.666
Race	**Caucasian** **African American** **Other** **Prefer Not to Say**	N (%) N (%) N (%) N (%)	37 (71.2) 10 (19.2) 3 (5.8) 2 (3.8)	33 (67.4) 8 (15.7) 5 (9.8) 5 (9.8)	34 (65.4) 11 (21.2) 5 (9.6) 2 (3.8)	x^2 0.59 [b] (Caucasian vs. All Others)	df 2	P 0.745
Ethnicity [a]	**Hispanic** **Non-Hispanic**	N (%) N (%)	8 (16.0) 42 (84.0)	8 (16.0) 42 (84.0)	7 (14.3) 42 (85.7)	x^2 0.07	df 2	P 0.964
Education [a]	**High School or Less** **Some College or More**	N (%) N (%)	16 (31.4) 35 (68.6)	13 (26.0) 37 (74.0)	10 (21.3) 37 (78.7)	x^2 1.29	df 2	P 0.525

a. Information is missing for some subjects.

b. Categories were combined to avoid invalid x^2 due to cells with expected count < 5.

Change in HAMD-17 Total Score from Baseline to Treatment Week 8 by Number of High Inflammatory Markers [a].

Inflammatory Group Based on Number of High Inflammatory Markers	Least-Square Means (se) of Change at Treatment Week 8			Significance of Treatment-by-Time Interaction	Standardized Treatment Effect Size at Treatment Week 8 [b]		
	EPA LS-Mean (se) [N]	DHA LS-Mean (se) [N]	Placebo LS-Mean (se) [N]	F df (P-Value)	EPA vs. PLA	DHA vs. PLA	EPA vs. DHA
4 or 5 High (N=21)	-11.14 (1.79) [10]	-4.90 (2.17) [7]	-5.02 (2.52) [4]	0.94 2, 79.8 (P=0.396)	- 1.11	+ 0.02	- 1.10
2 or 3 High (N=38)	-12.38 (1.47) [13]	-11.52 (1.35) [13]	-9.43 (1.35) [12]	0.70 2, 135 (P=0.498)	- 0.59	- 0.44	- 0.17
1 High (N=50)	-11.76 (1.28) [13]	-7.31 (1.11) [17]	-10.80 (1.10) [20]	1.20 2, 177 (P=0.303)	- 0.20	+ 0.73	- 0.97
0 High (N=46)	-7.78 (0.85) [16]	-11.65 (0.96) [14]	-10.85 (0.83) [16]	4.09 2, 215 (P=0.018)	+ 0.91	- 0.23	+ 1.11

a. MMRM analysis of N=155 evaluable subjects with all five biomarkers at baseline.

b. By Cohen's d effect size = (difference between LS-Mean change) / pooled sd for each pair of treatments (sd

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

Flow of Randomized Subjects by Treatment Group

Subject Status	1g/day	2g/day	4g/day	Placebo	Total
Randomized (n)	15	15	16	15	61
Evaluable (n)	15	14	16	12	57
% of Those Randomized	100.0%	93.3%	100.0%	80.0%	93.4%
Analyzable Data to Visit 9 (Treatment Week 12) (n)	14	11	13	10	48
% of Those Randomized	93.3%	73.3%	81.2%	66.7%	78.7%

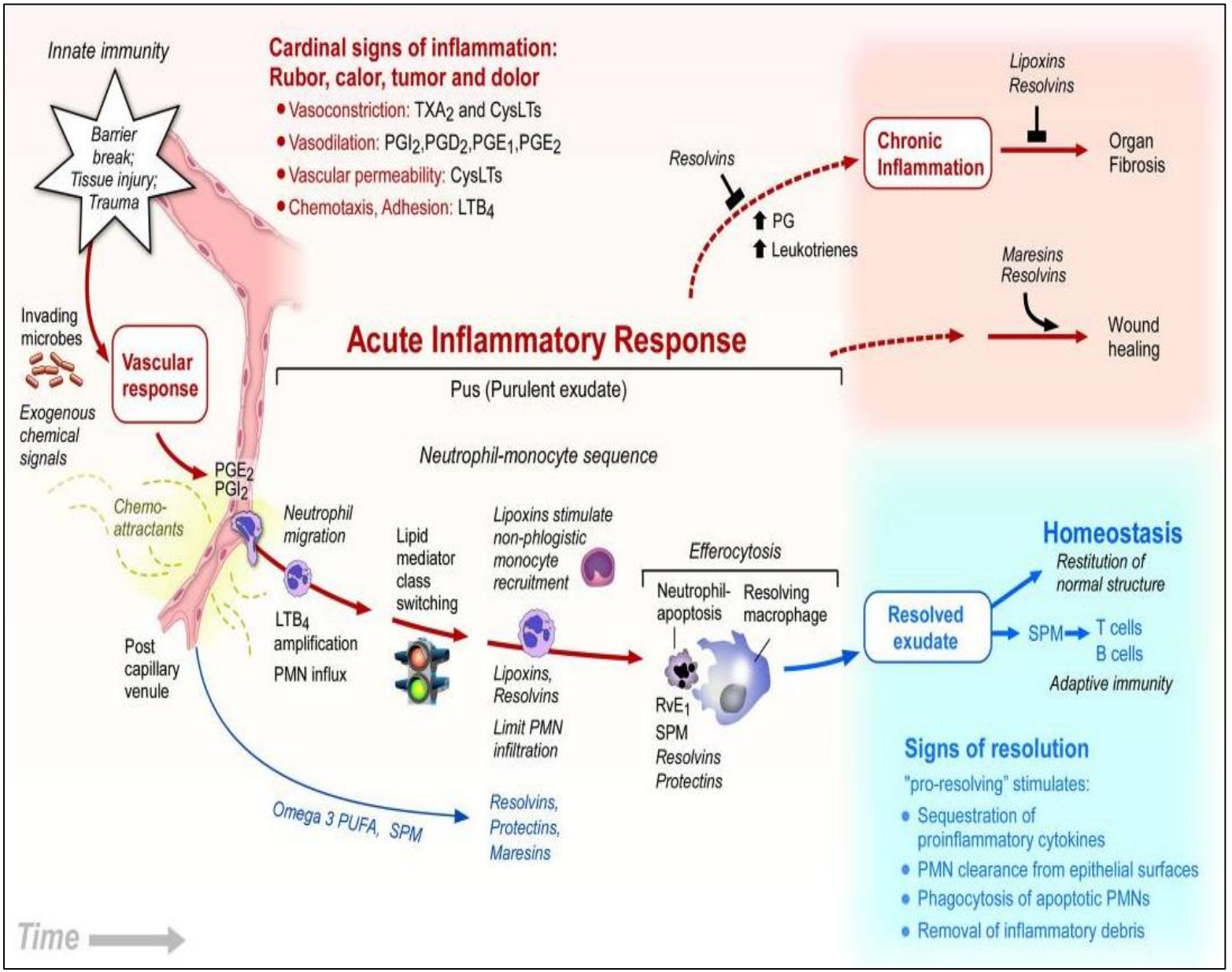
IDS-C30 Response (≥50% Reduction in Total Score) (n=48 Completers)

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

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

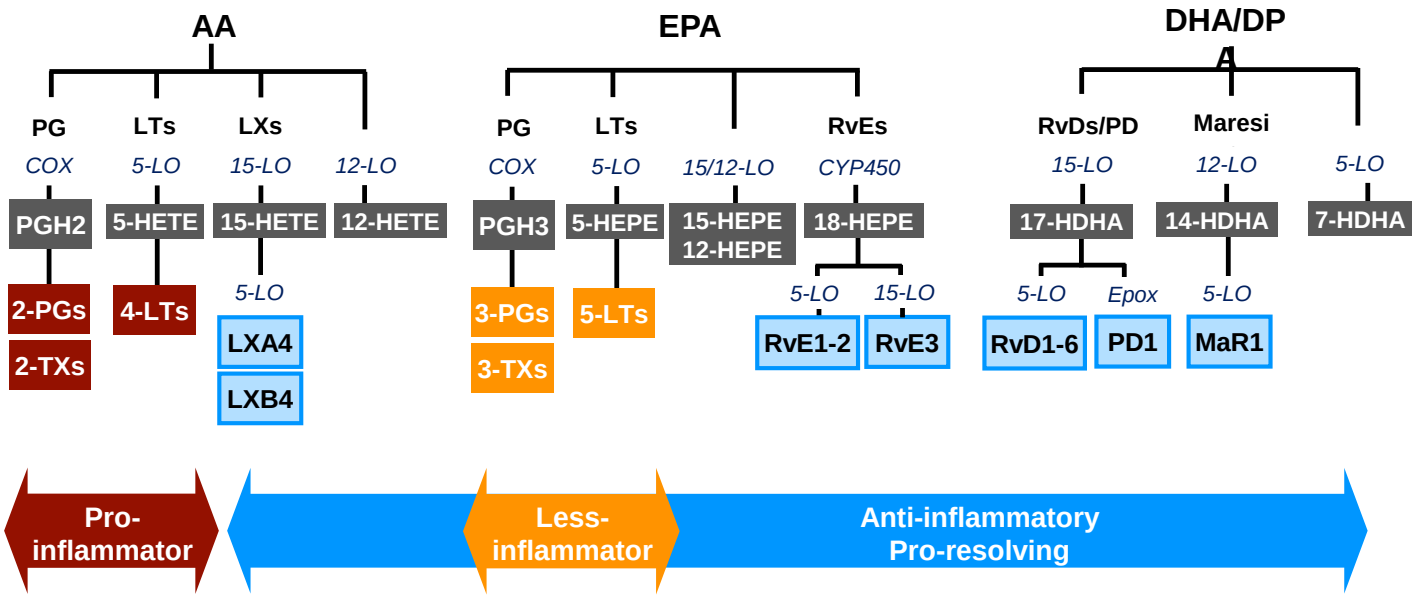
Percent Change from Baseline	Spearman Rank-Order Correlation with Percent Change in IDS-C30 at Treatment Week 12 (Correlation, p=value, and n)			
	1g/day	2g/day	4g/day	Placebo
Plasma hs-CRP	-0.129 p=0.694 13	-0.091 p=0.790 n=11	0.753 p=0.003 13	0.164 p=0.652 10

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

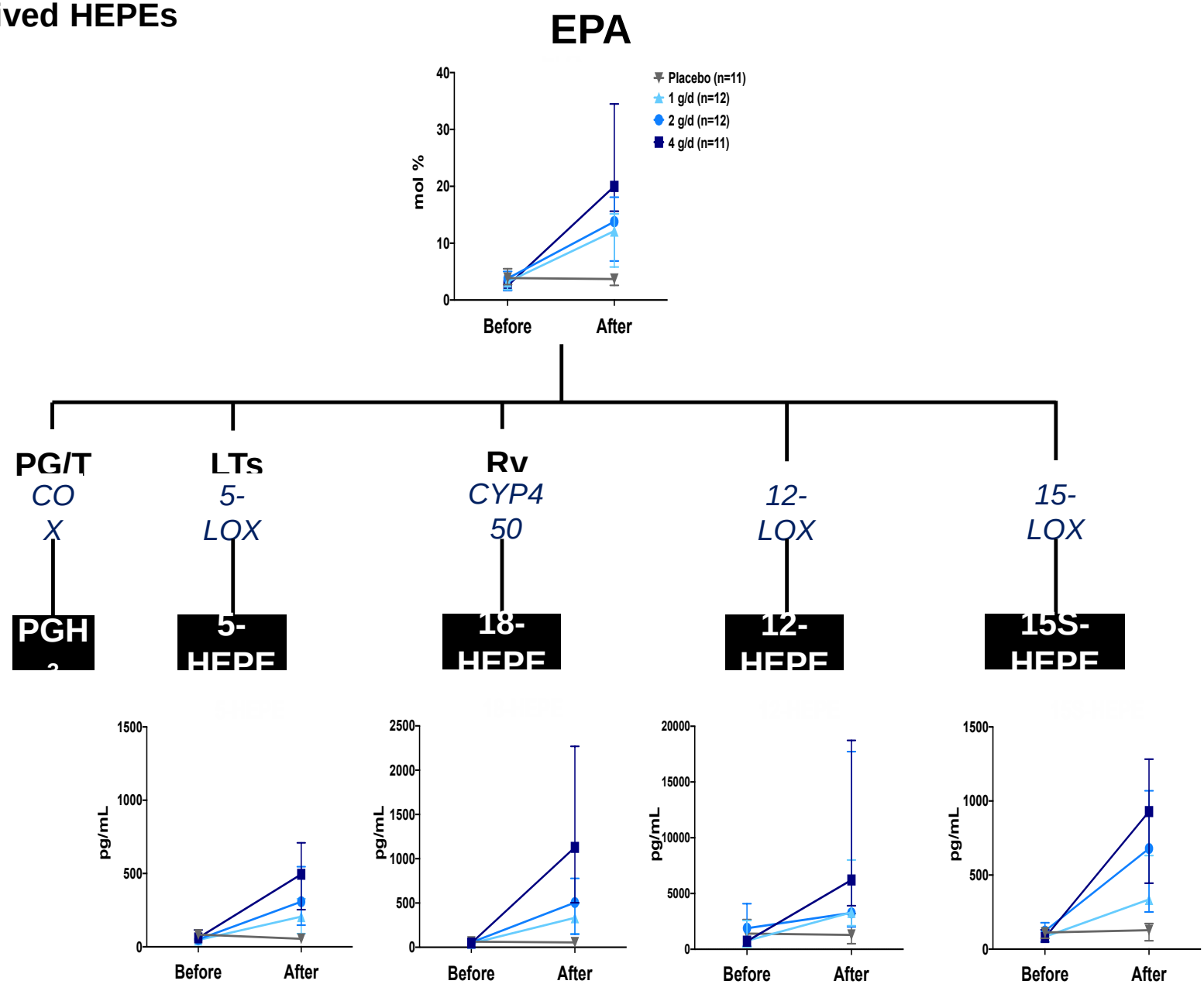


Serhan (2014) *Nature* 510(7503): 92-101. PMCID: PMC4263681.

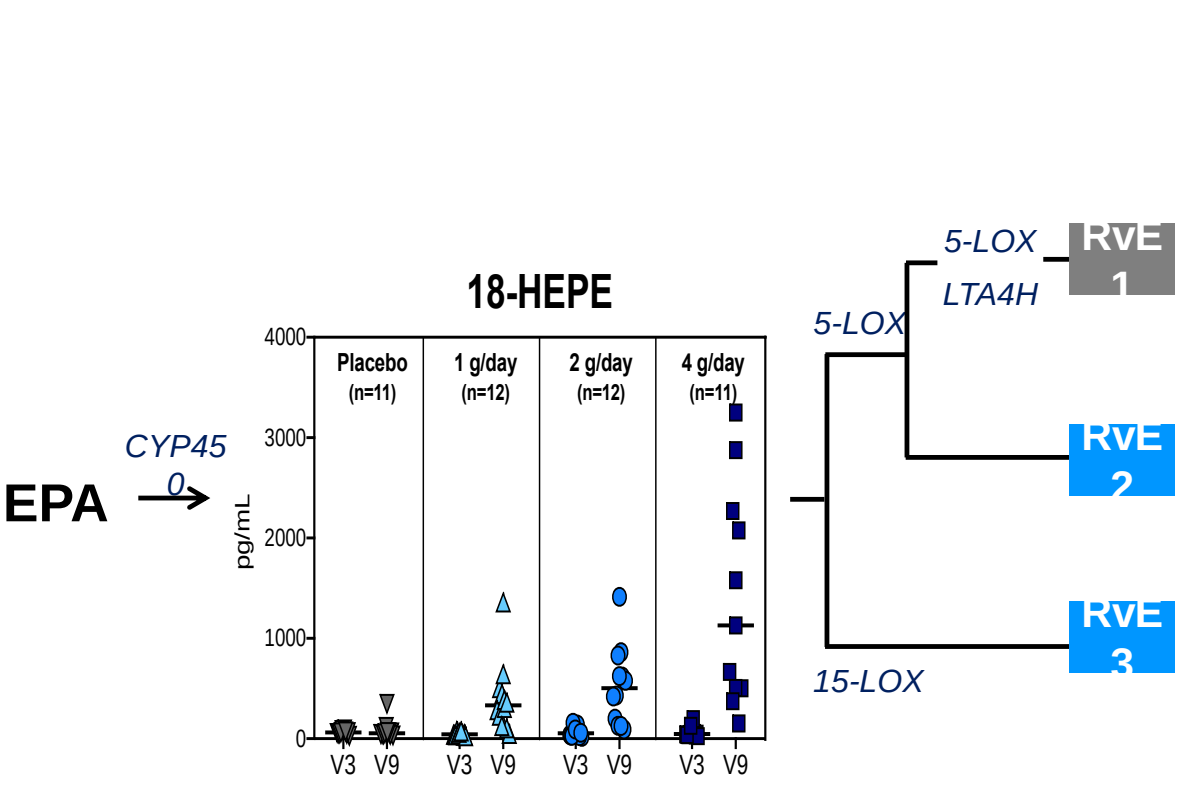
SPM biosynthetic pathways

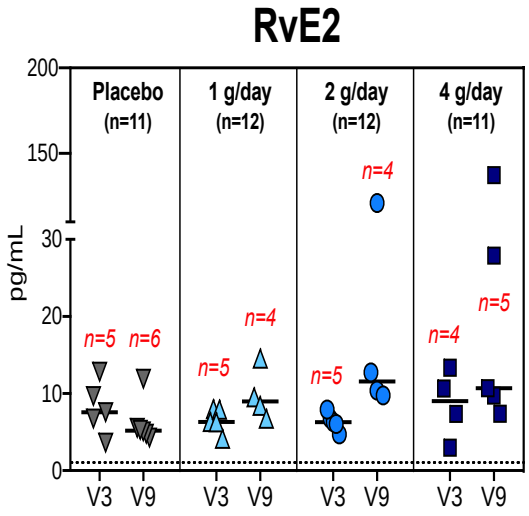


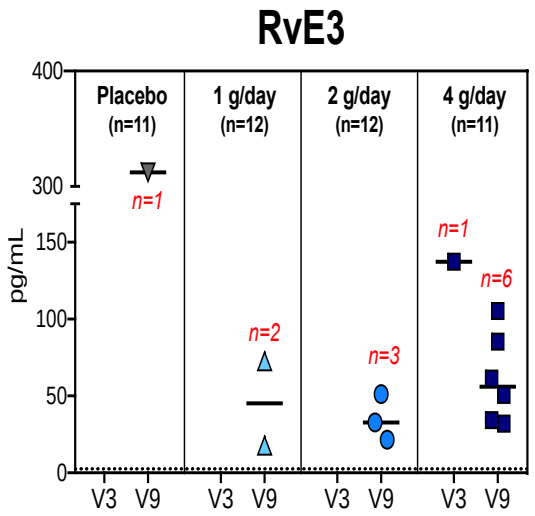
EPA-derived HEPEs



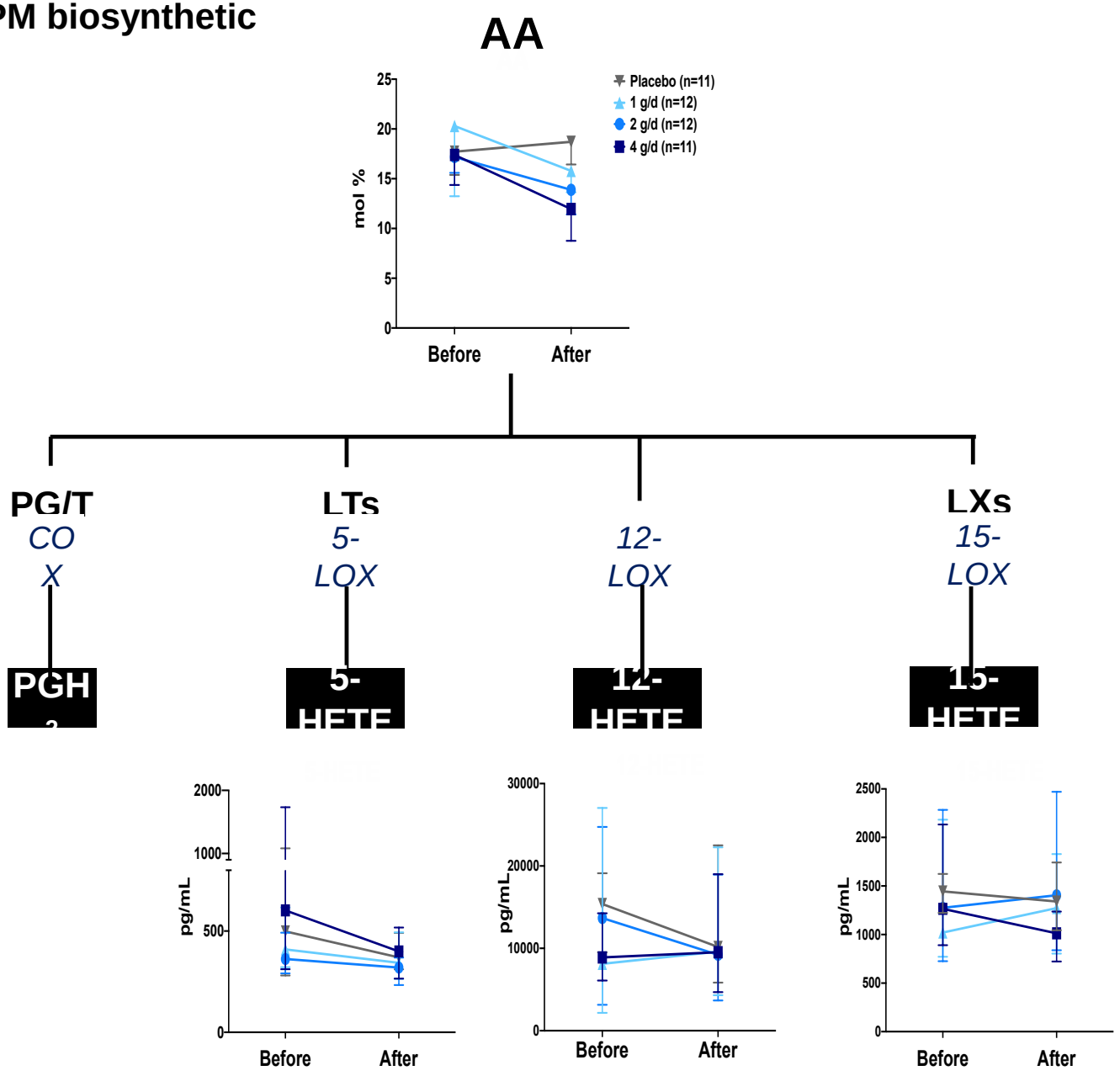
EPA-derived RvEs



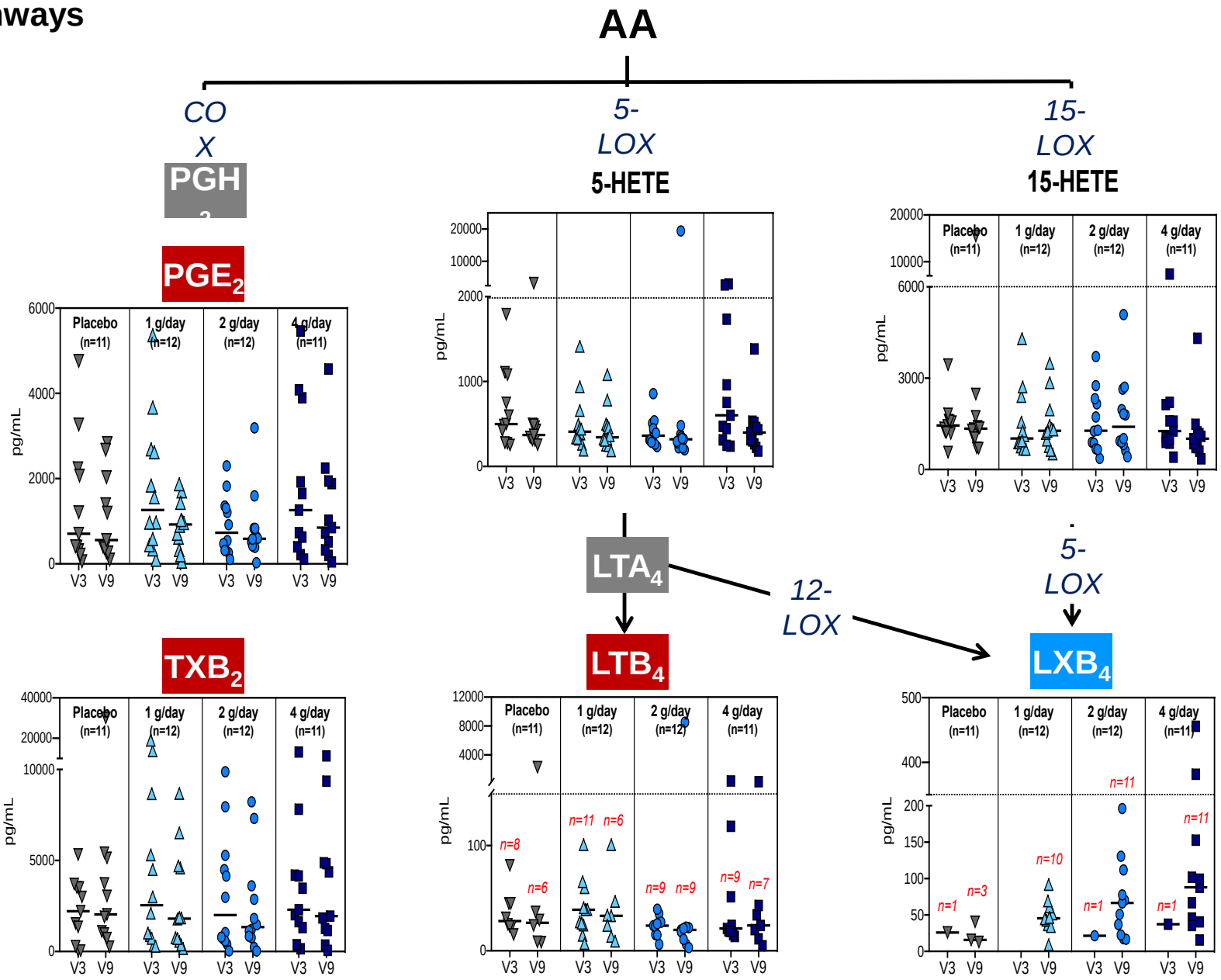




AA-derived SPM biosynthetic pathways



AA-derived SPM biosynthetic pathways

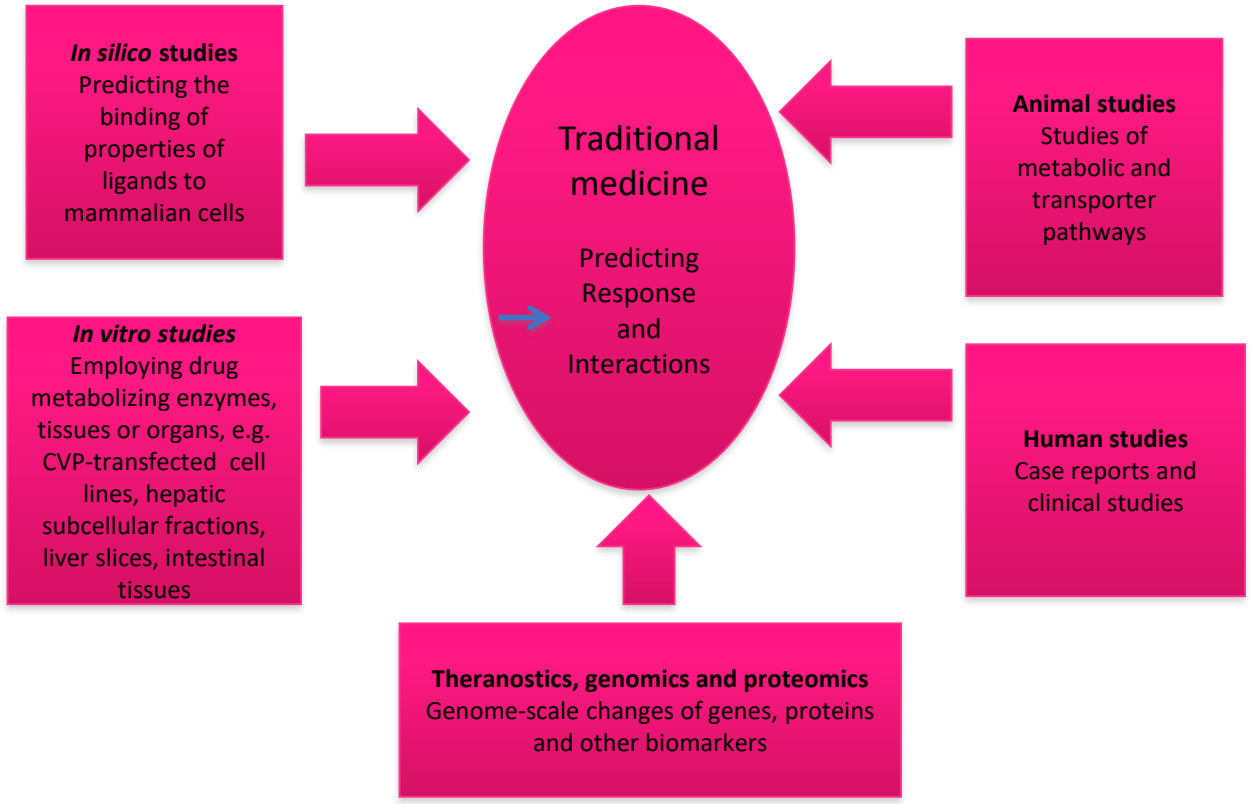


Our work with natural products suggest

There needs to be rigorous investigation of:

a. The composition of the compound being tested
    a. What component of the plant?
    b. Purity of the formulation
    c. Stability of the formulation
b. The question being investigated
    a. Is it too broad to be informative?
    b. Are the correct measures being employed?
    c. Over-inclusive analysis plans
c. The toxicity of the compound
    a. Natural is not necessarily safe
    b. The unexpected happens!
d. The mechanism of action being evaluated
    a. You have to “place your bet” to design the appropriate experiment
e. The composition of the study population
    a. Heterogeneity may obscure an effect
f. Unexpected findings

Where research needs to go



Modified from work by Hu M, Fan L, Hong-Hao Z and Tomlinson B. *Theranostics meets traditional Chinese medicine: rational prediction of drug-herb interaction*. Exper Rev Mol Diagn 12(8), 815-830 (2012)

Resources for reviewing integrative medicine therapies

- Summaries.cochrane.org – The Cochrane Collaboration is an international, independent, not-for-profit organization
- NCCIH.nih.gov – The National Center for Complementary and Integrative Health
- **www.consumerlab.com** – independent test results and information to help consumers and healthcare professionals identify the best quality health and nutrition products
- **www.umm.edu/health/medical/altmed** - University of Maryland – free
- **http://naturaldatabase.therapeuticresearch.com** – Evidence based science on integrated, complementary and alternative therapies
- **https://www.healthwavehq.com** – Fullscript – allows clinicians to "write a prescription" for preferred supplements