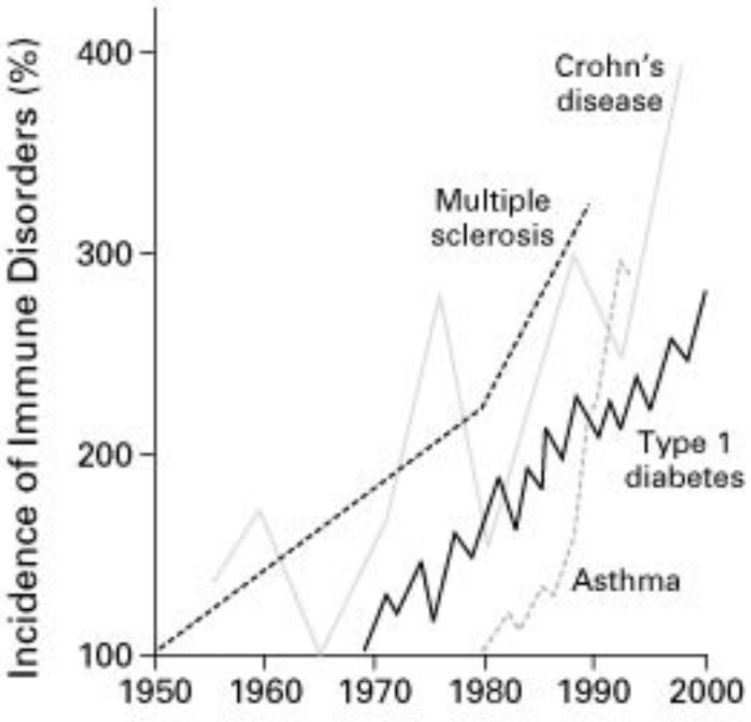
Understanding the Environmental Determinants of Host Fitness to Inflammation

Andrew Wang
Yale University
Medicine | Immunobiology

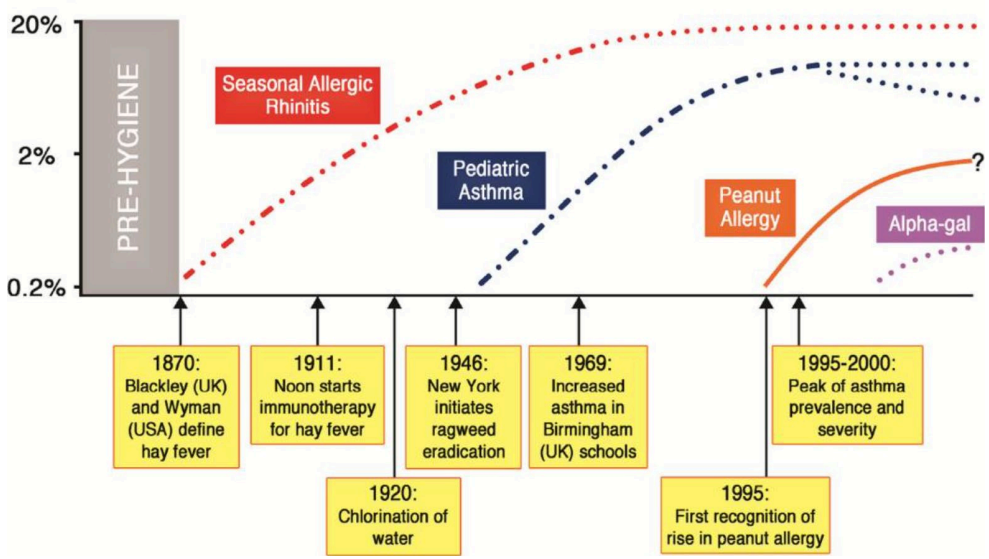
Disclosures

I consult or receive funds from: NGM Biopharmaceuticals, Soleil Bio Labs, The Column Group, Seranova, and AstraZeneca

Why is the prevalence of autoimmune/allergic diseases increasing?

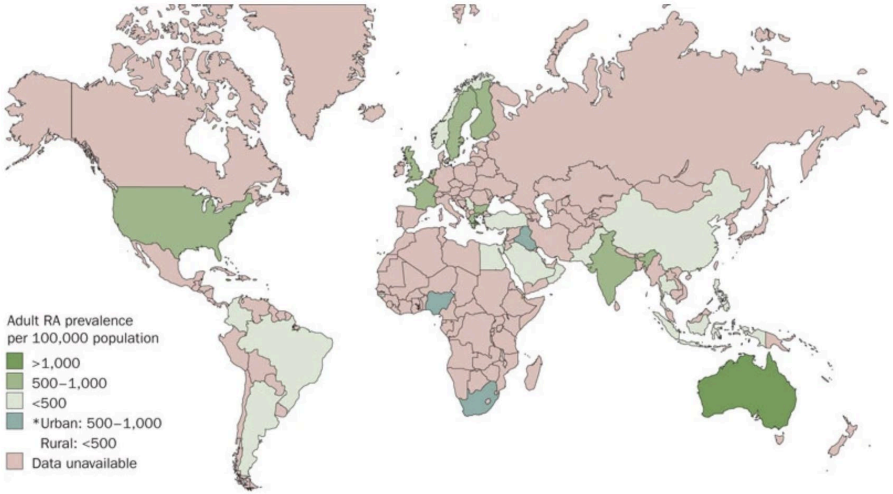


Bach. NEJM. 2002.

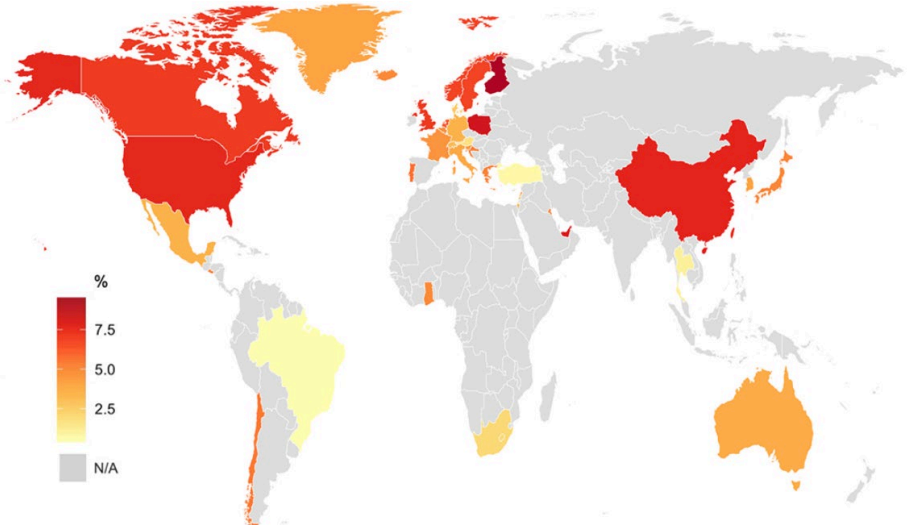


Platts-Mills. JACI. 2015.

Increases tend to occur only in modern industrialized environments

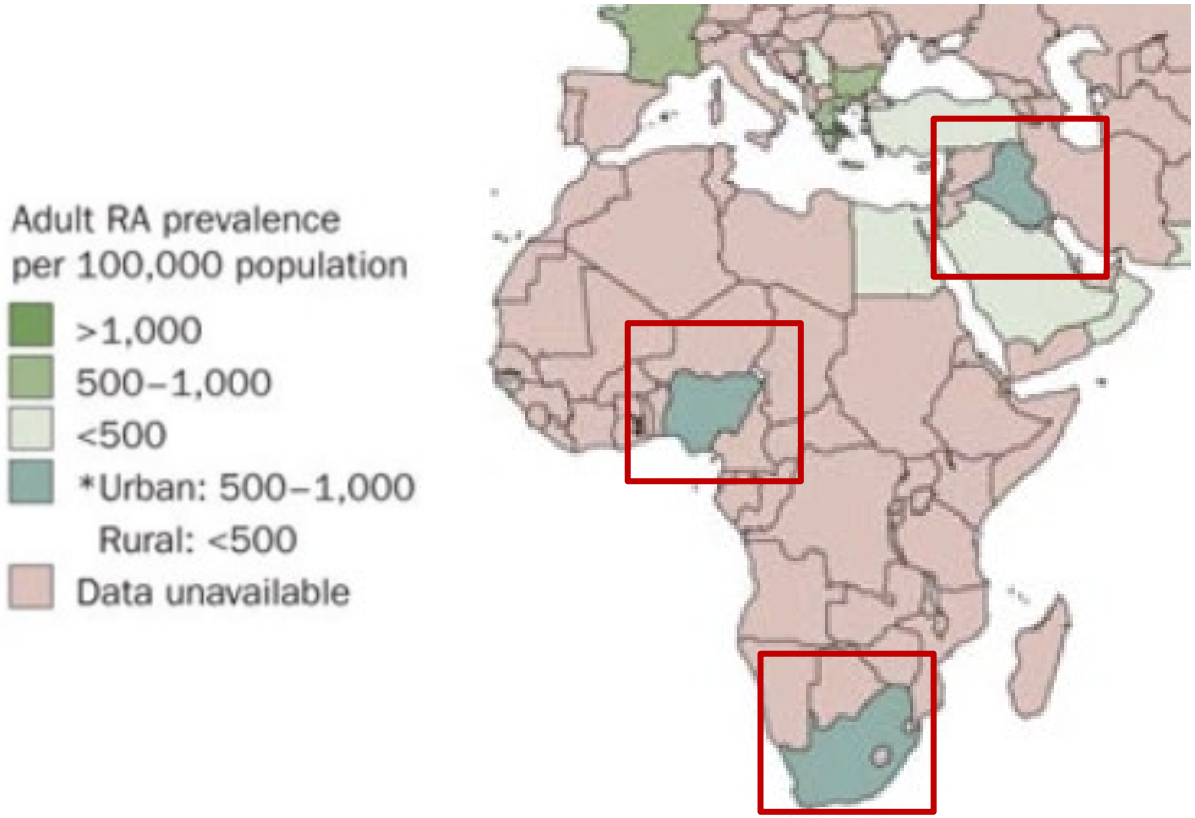


Shapira. Nat Rev Rheum. 2010



Warren. Cur Allergy Asthma Rep. 2020

Increases tend to occur only in modern industrialized environments



Incomplete penetrance and a role for the "environment"?

Table 1. Relative risks in autoimmune disease

Disease	Concordance rate (%)			Population prevalence (%)	λs
	Monozygotic twins	Dizygotic twins	Non-twin siblings		
IMD	30–50	0–13	6	0.4	15[a]
MS	25	0–5	3–5	0.1	20[b]
SLE	24–57	2–5	2–5	0.2	20–40[c]
RA	12–15	3–4	2–4	0.24–1.0	5–10[d]

[a]Refs. 106 and 107. [b]Ref. 49. [c]Ref. 108. [d]Ref. 3.

Wanstrat. Nature Immunol. 2001.

Table I Concordance rates for peanut allergy

	Monozygotic	Dizygotic
Concordant	9	3
Discordant	5	41
Pairwise concordance rate*	64.3%	6.8%

* $\chi^2 = 21.38$; $P < .0001$.

Sicherer. JACI. 2000.

Divergent trajectories in MZ twins in the same environment

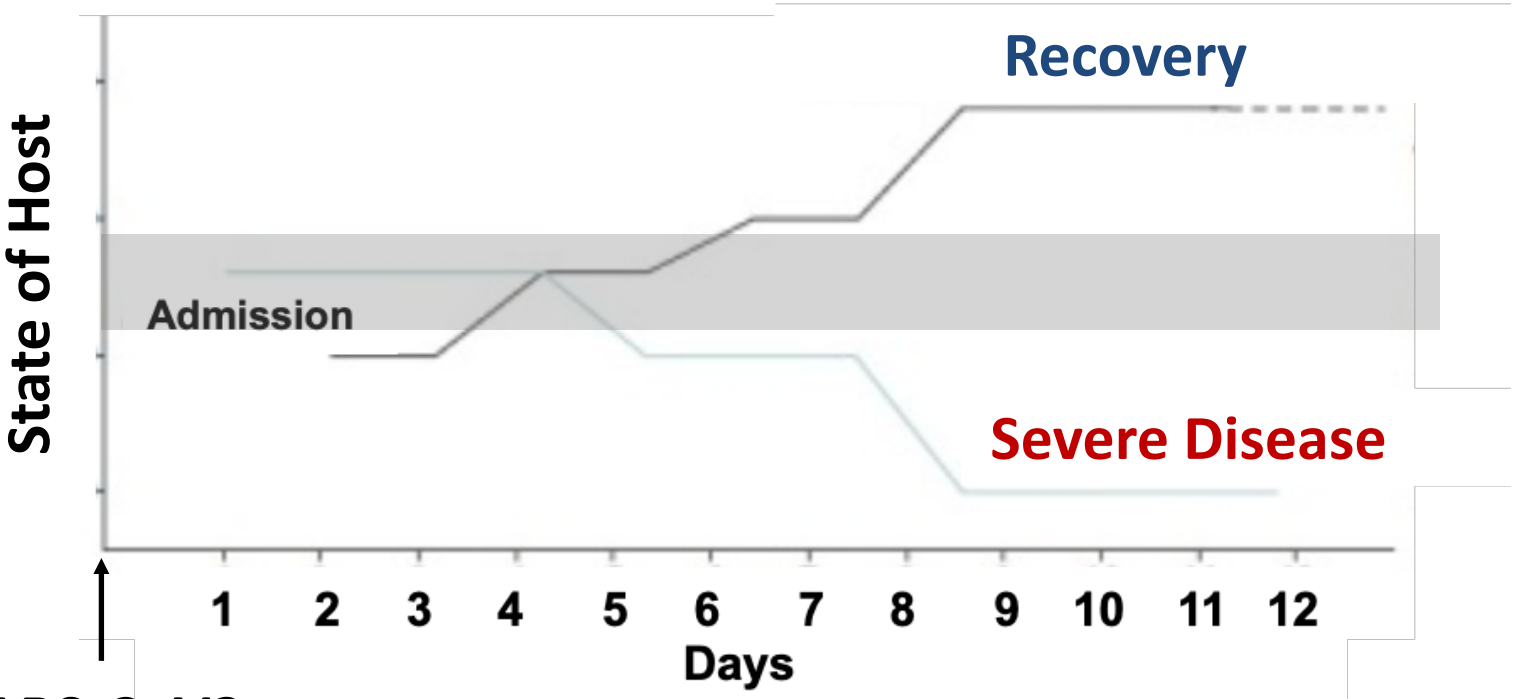
Annals of Internal Medicine

Letters | May 2021

OBSERVATION: CASE REPORT

Davide Lazzeroni, MD, Pietro Concari, MD, and Luca Moderato, PhD

Simultaneous COVID-19 in Monozygotic Twins



The curious case of LD50

The Error of Determination of Toxicity.

By J. W. Trevan, Wellcome Physiological Research Laboratories, Beckenham, Kent.

(Communicated by Dr. H. H. Dale, Sec. R.S.—Received March 26, 1927.)

VII. *Discussion.*

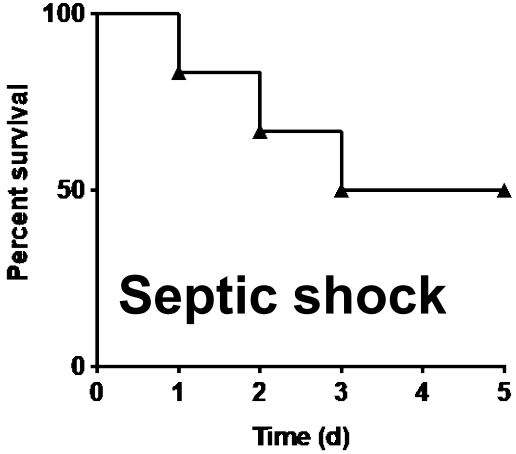
A few points of general interest remain to be cleared up.

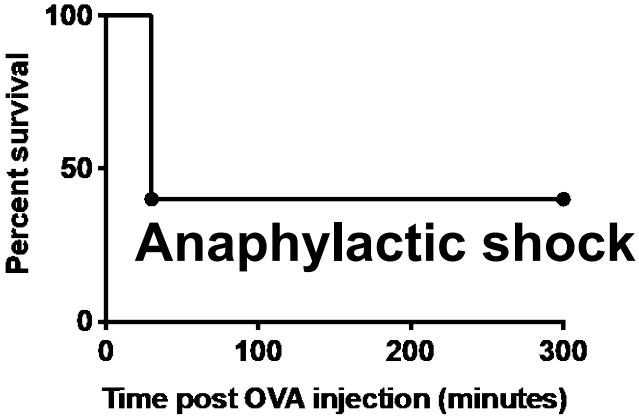
(1) The form of a characteristic depends on the combined effect of a large number of different factors, some of which are controllable by alteration of experimental conditions (see, for instance, the remarkable effect of temperature on the response of mice to insulin—Trevan and Boock, 1926) and most of which are not. Among the former is probably the effect of heredity.

It is almost certain that animals inbred, after the fashion of the Wistar Institute rats, will give steeper characteristics than casual groups selected at random from the ordinary dealers' stocks. The effects of colour and weight on the insulin curve have, however, been found to be negligible (Trevan and

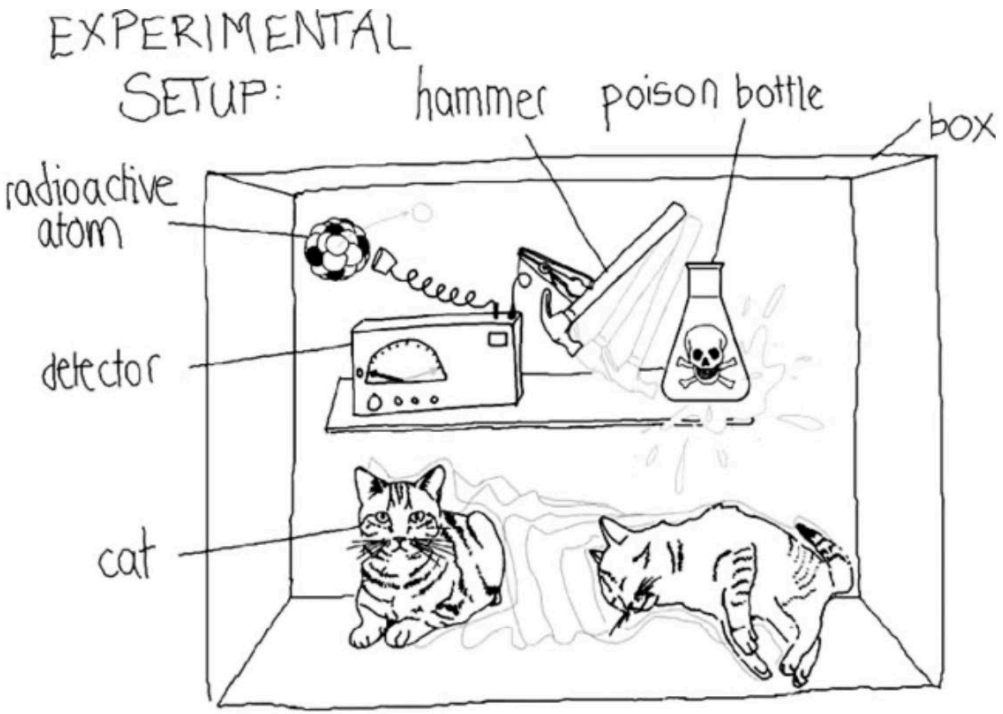
LD50: Are there differences in the environment?

The Paradox of Lethal Dose 50





Schrôdinger's Cat
Our Mice



E. Schrôdinger. Naturwissenschaften. 1935.
Schleich et al. Applied Physics B. 2016.

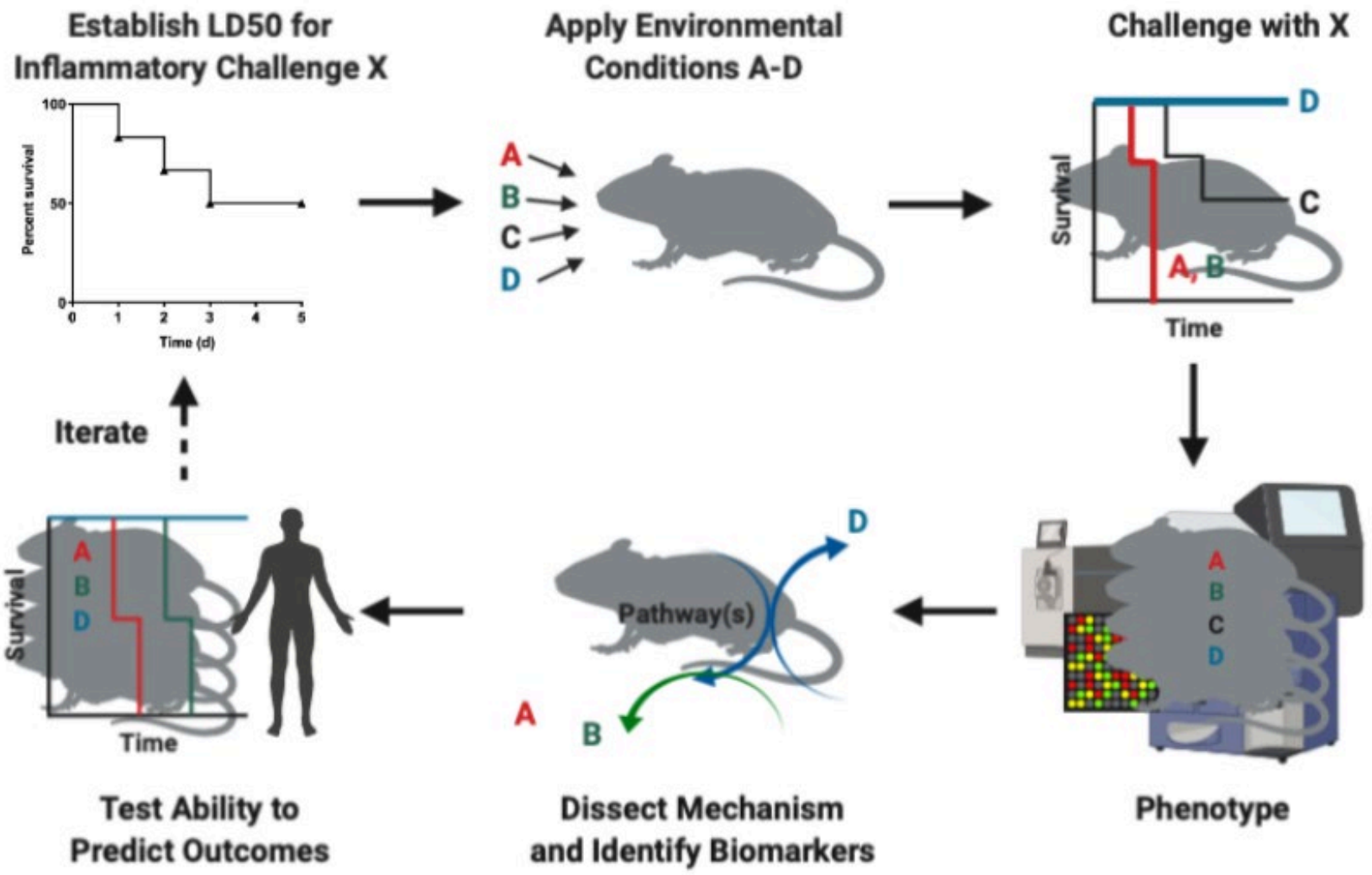
Questions

If the “environment” matters, what in it, exactly, matters?

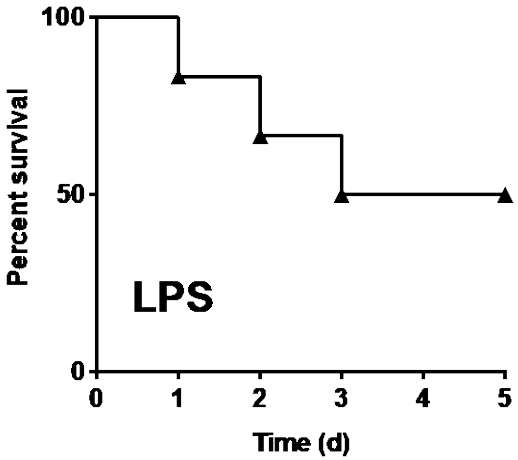
Using LD50 models pre-clinically, what, exactly, are we modeling?

Are disease trajectory divergences random or knowable?

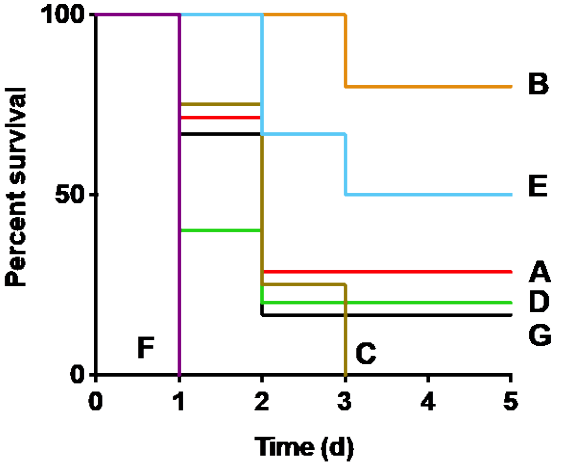
Approach #1: Hypothesis-driven "screen" of the (micro)environment



Maximization of acute psychological stress leads to LD100

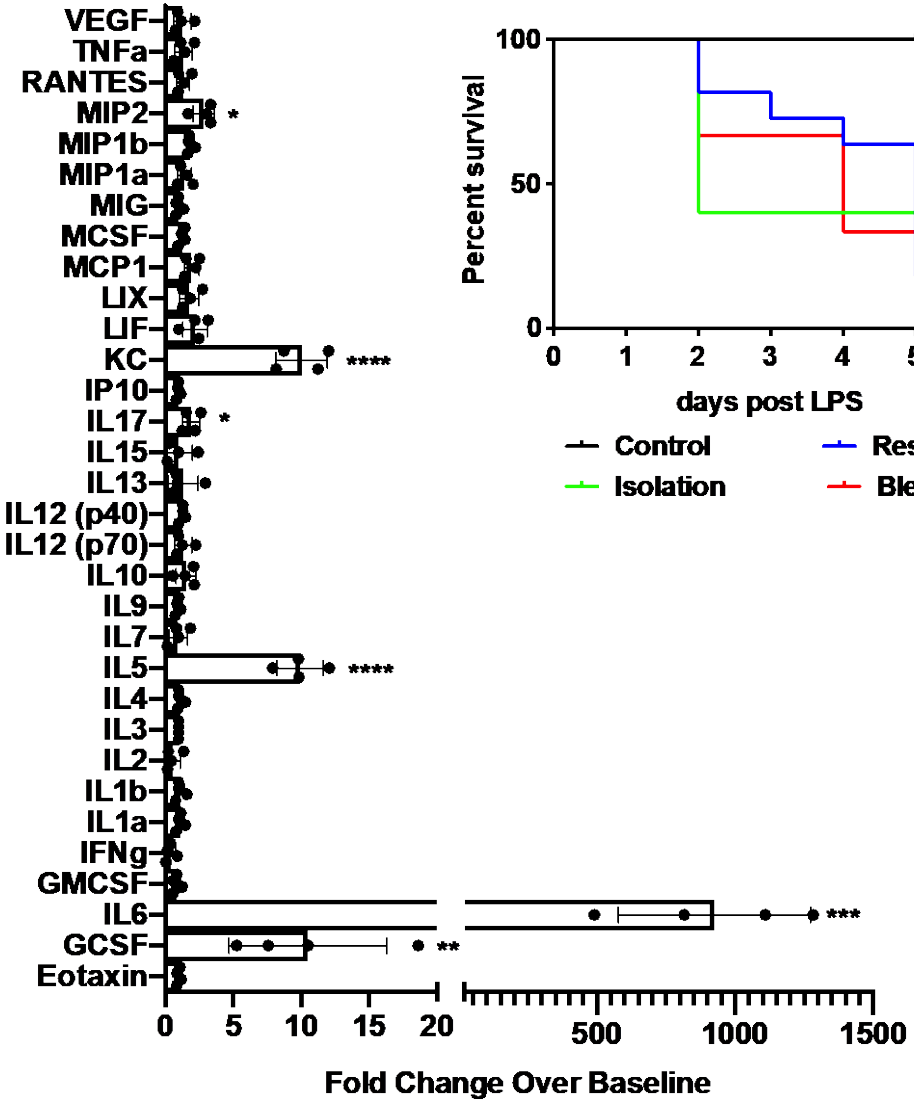


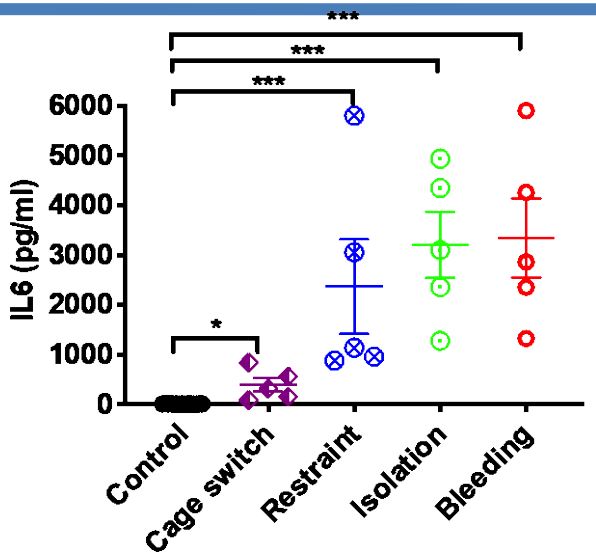
A. Fast
B. Cold
C. Restraint
D. Isolation
E. Prior LD0 LPS
F. Prior LD0 Poly I:C
G. Sleep deprivation

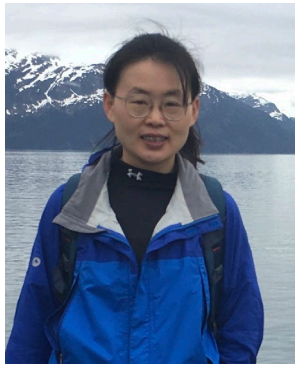


Unpublished.

Acute psychological stress induces cytokines



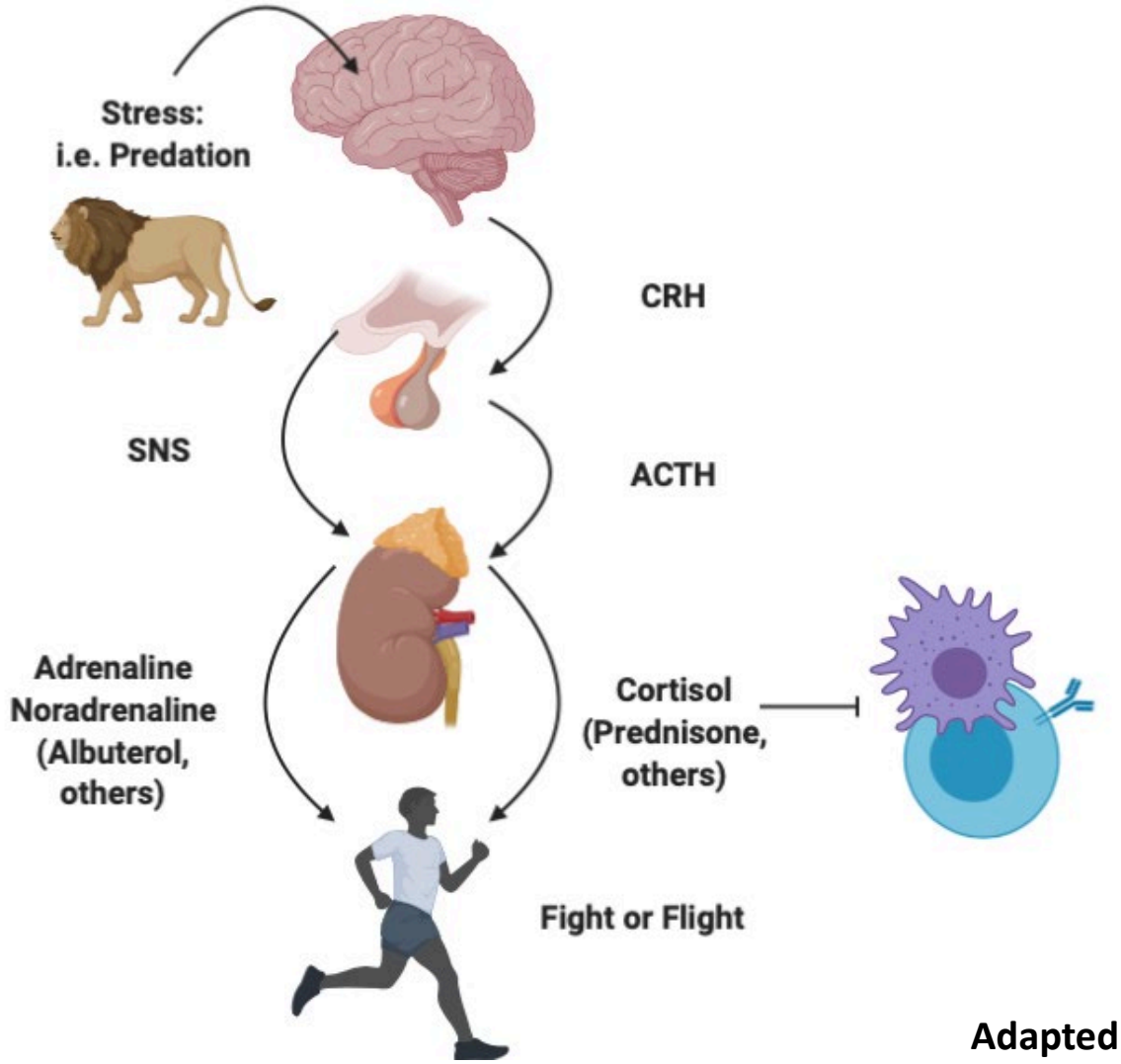




Hua Qing

Reina Desrouleaux

Acute Stress Increases Immunosuppressants

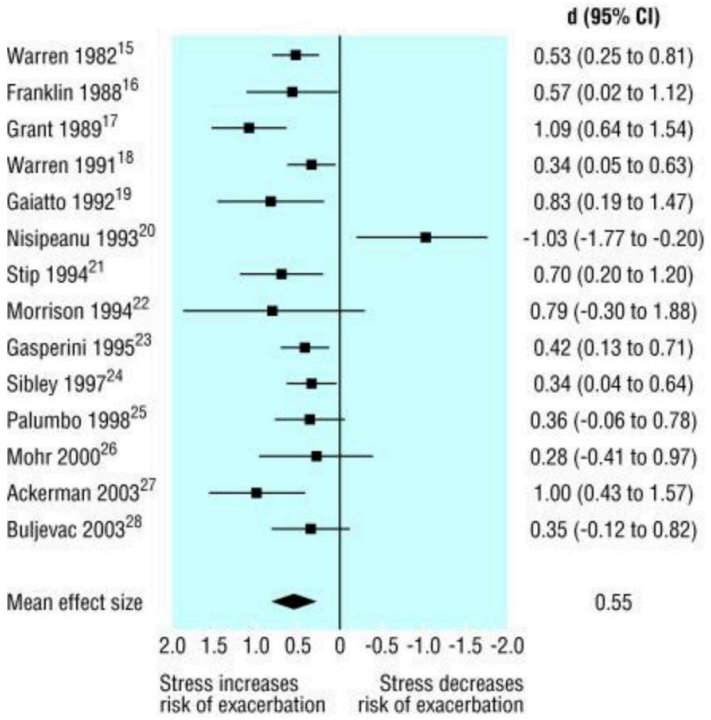


Adapted from:
Wang et al. Science 2019.

Paradox: Acute Stress Worsens Inflammation

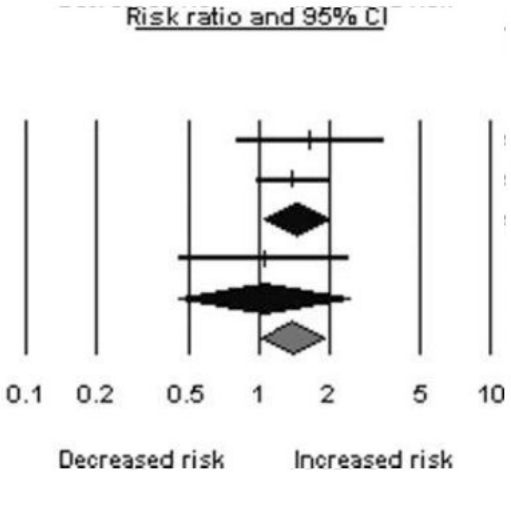
"To avoid the fever, one should guard himself against his own anger." Hippocrates 4th Century

Multiple Sclerosis



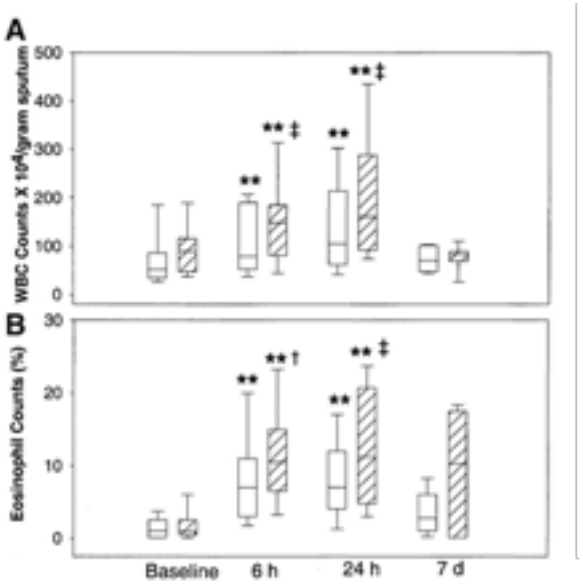
Mohr et al. BMJ. 2009.

Cancer



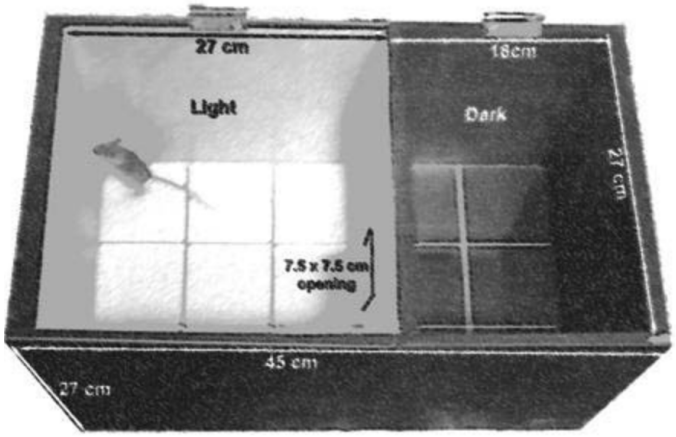
Satin et al. Cancer. 2009.

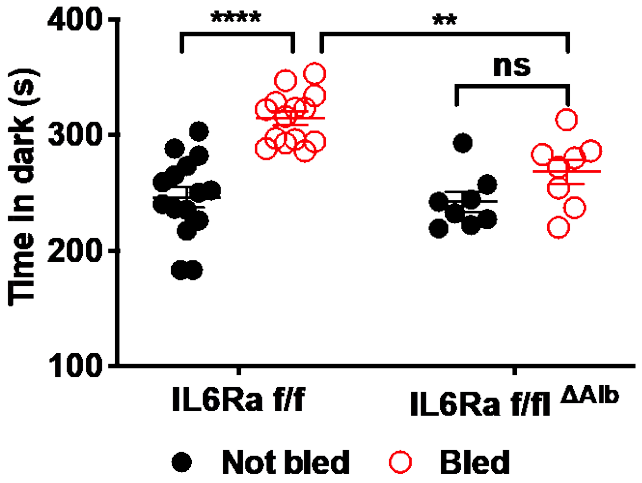
Asthma



Liu et al. Am J Respir Crit Care Med 2002.

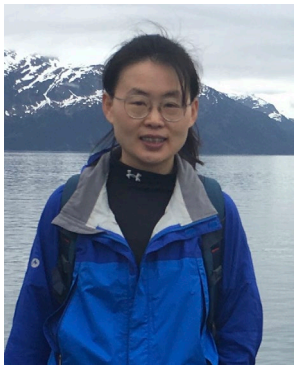
Hepatic IL6 Signaling is Required for Flight Behavior





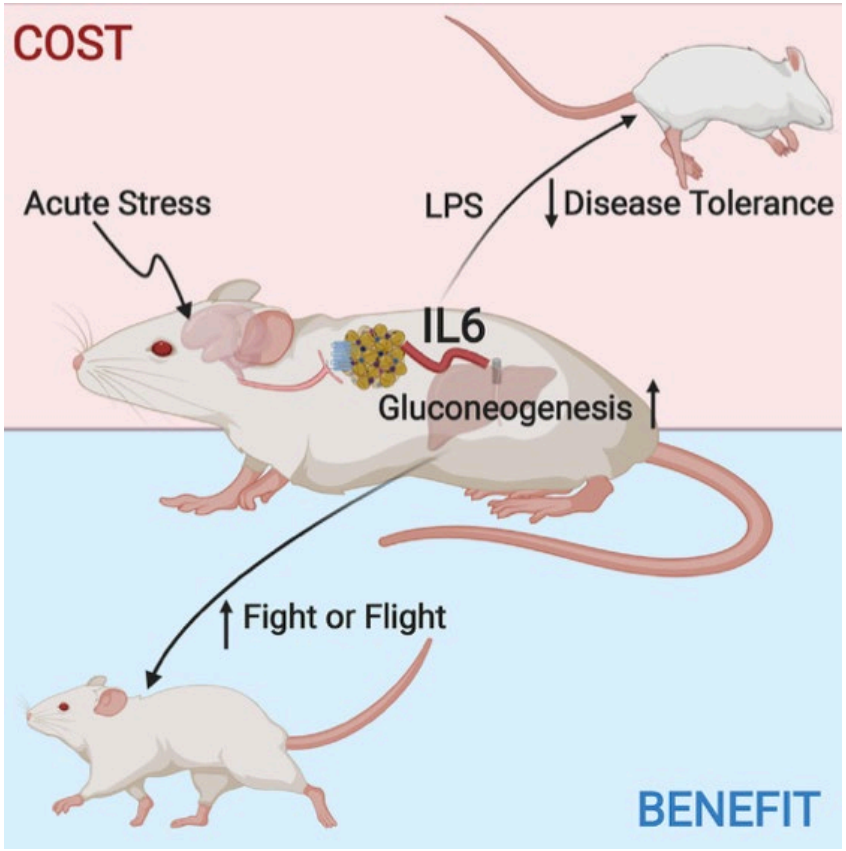
Qing, Desrouleaux, et al. *Unpublished*

Psychological stress induces adaptive inflammation (that comes at a cost)



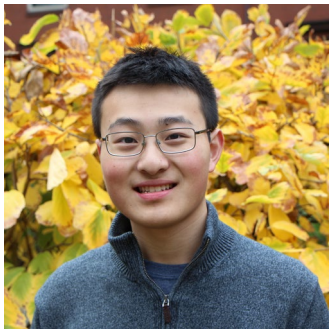
Hua Qing

Reina Desrouleaux



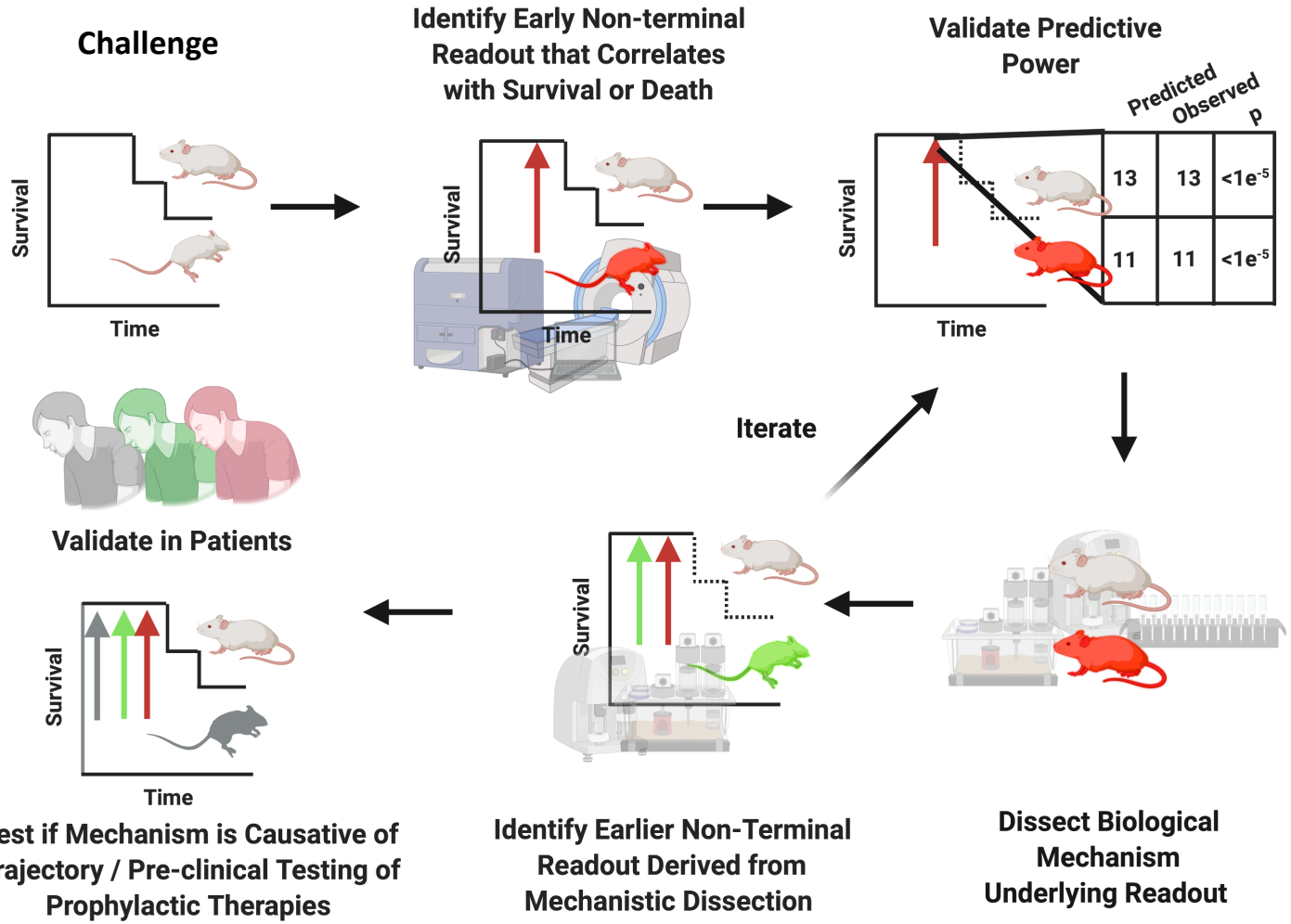
Qing, Desrouleaux et al. Cell. 2020.

Approach # 2: ”Reverse Engineering” LD50



Michael Gao

Kavita Israni-Winger



Gao, Israni Winger et al. *In revision.*

Approach #3: “Screening” the modern environment for adjuvants

NOT-FOE

Antigen
(like self proteins or food proteins)

+

=

Immune Tolerance

FOE

Antigen
(like spike protein)

+

Adjuvant
(like viral components or added compounds in vaccines)

=

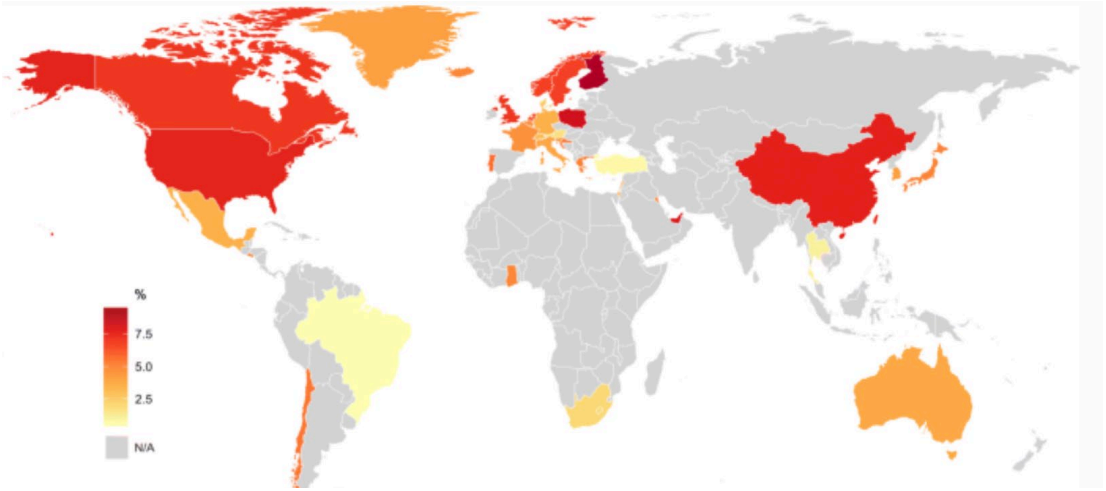
Immune Memory

Adjuvants in broad strokes

Type I	Type II
Complete Freund's Adjuvant	Aluminum salts (Alum)
LPS	Cholera Toxin
Squalene	Chitin
Flagellin	Papain
Poly(I:C)	Plant lectins
Lipid A analogues – MPL, RC529, GLA	Ara h 1
Imiquimod	Bioactive lipids
Emulsions (MF59)	

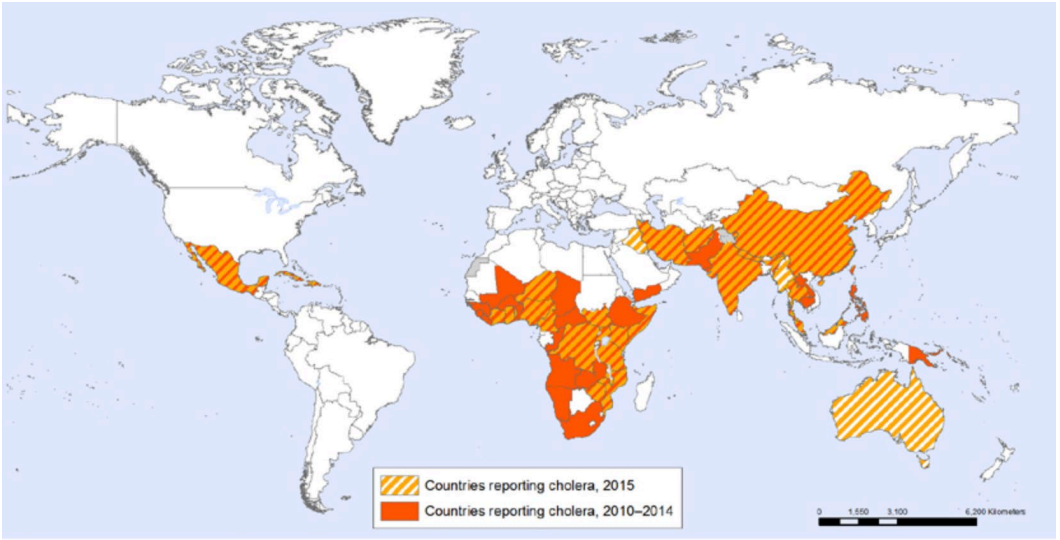
Cholera and food allergy prevalence don't overlap

Food Allergy



Warren et al. Current Allergy. 2020.

Cholera



WHO

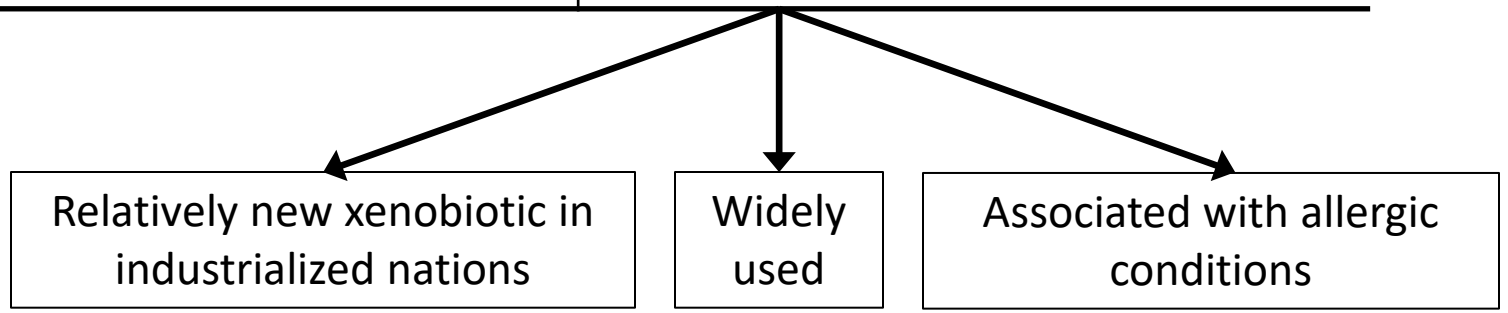
Molecular features (if there are one/many) that confer allergic adjuvancy are unknown

Pattern Recognition Receptors **?**

Type I	Type II
Complete Freund's Adjuvant	Aluminum salts (Alum)
LPS	Cholera Toxin
Squalene	Chitin
Flagellin	Papain
Poly(I:C)	Plant lectins
Lipid A analogues – MPL, RC529, GLA	Ara h 1
Imiquimod	Bioactive lipids
Emulsions (MF59)	

Something new?

Type I	Type II
Complete Freund's Adjuvant	Aluminum salts (Alum)
LPS	Cholera Toxin
Squalene	Chitin
Flagellin	Papain
Poly(I:C)	Plant lectins
Lipid A analogues – MPL, RC529, GLA	Ara h 1
Imiquimod	Bioactive lipids
Emulsions (MF59)	New Environmental Factor?



Approach #3: “Screening” the modern environment

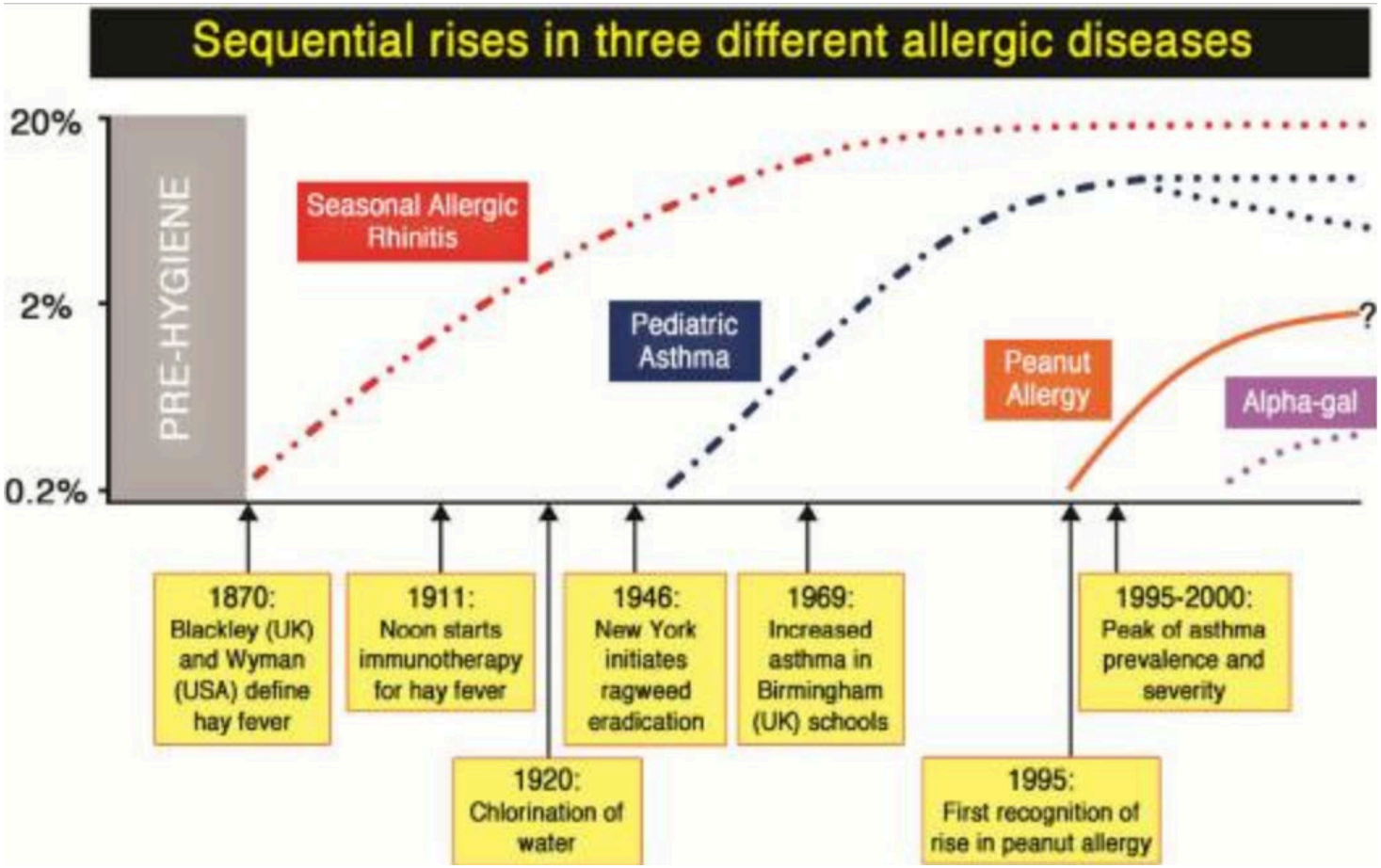
Pre-1960	Post-1960
Antigen (peanut, dust mite, ovalbumin, ovomucoid, etc.)	Antigen (peanut, dust mite, ovalbumin, ovomucoid, etc.)
+	+
Manmade xenobiotics	Manmade xenobiotics
=	=
Allergic sensitization	Allergic sensitization

Approach #3: “Screening” the modern environment

Anna Eisenstein

Brandon Hilliard

Dan Waizman



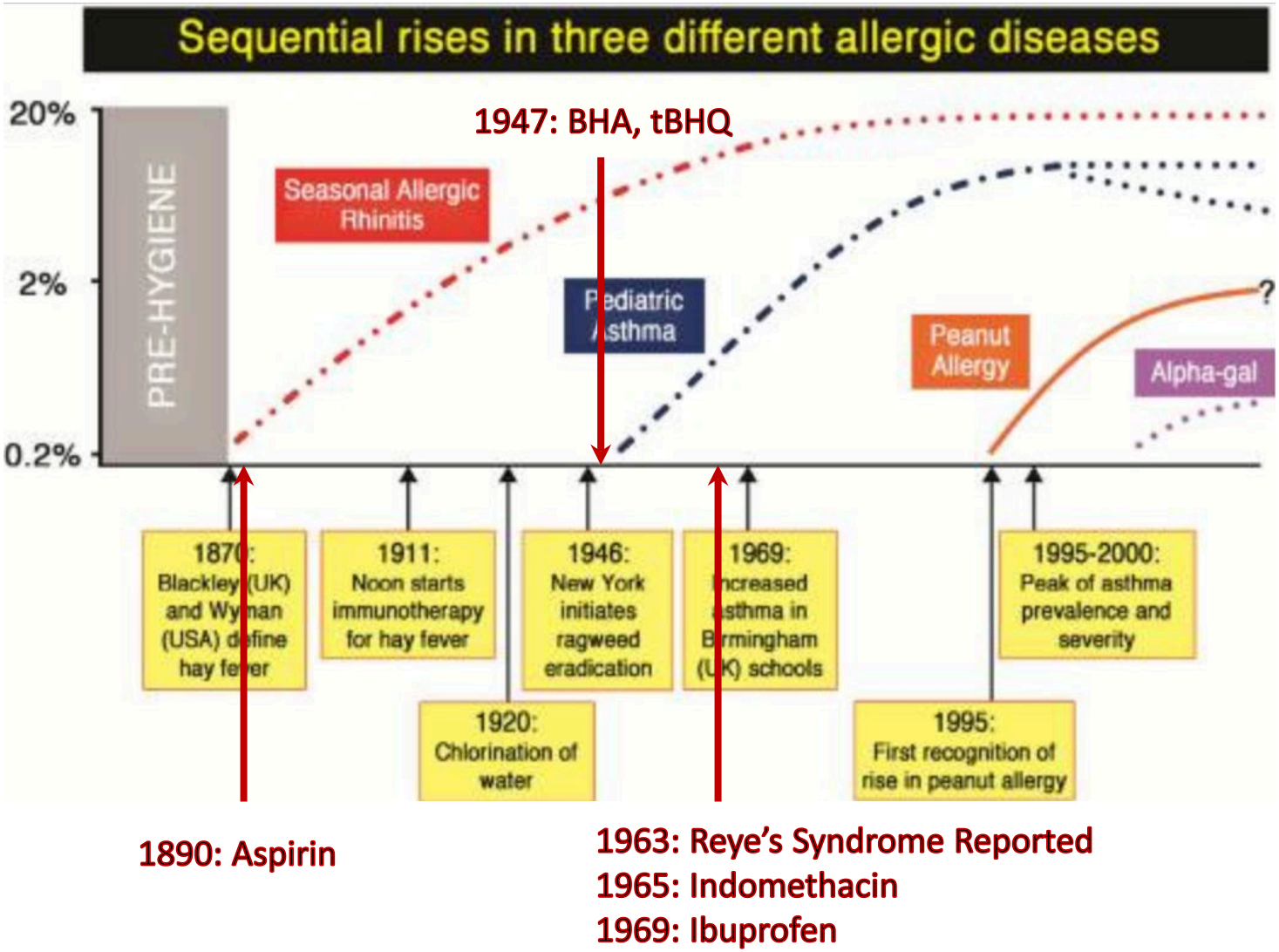
Platts-Mills. JACI. 2015.

Approach #3: “Screening” the modern environment

Anna Eisenstein

Brandon Hilliard

Dan Waizman



Bastardizing (mea culpa) the beautiful figure from Platts-Mills. JACI. 2015.

The Screen

An official website of the United States government Here's how you know

FDA U.S. FOOD & DRUG ADMINISTRATION

← Home / Food / Food Ingredients & Packaging / Food Additives & Petitions / Food Additive Status List

Food Additive Status List

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Food Additives & Petitions

- Color Additives in Food
- Food & Color Additive Petitions
- Food Additive Status List
- Substances Added to Food (formerly EAFUS)

Color Additive Status List

Disclaimer FDA offers this list as a service to the Field Offices. Inclusion of a substance in the Food Additive Status list does not necessarily represent its legal regulatory status. The regulations for food additives in 21 Code of Federal Regulations need to be consulted.

More >>

Forward | Abbreviations

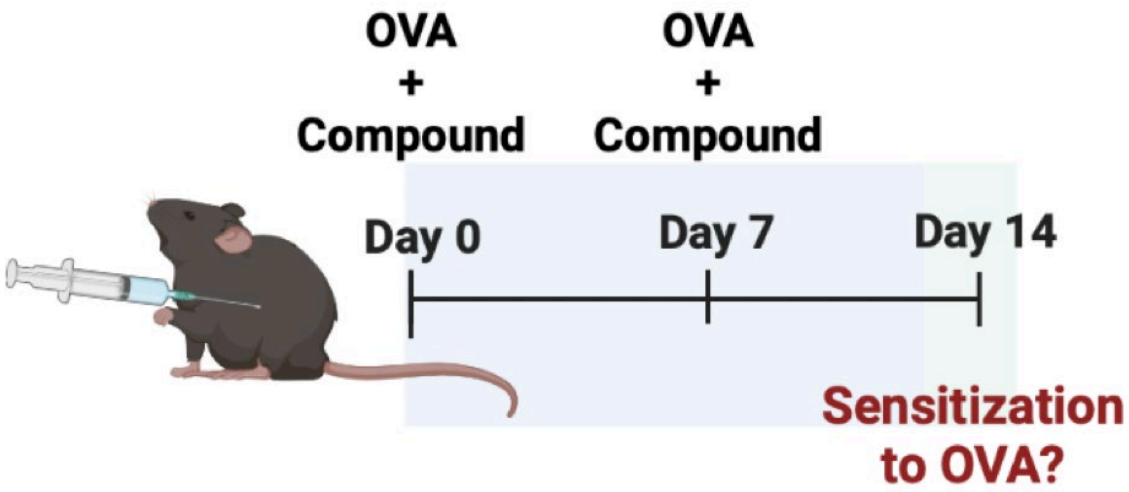
Additives: A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

FOREWORD

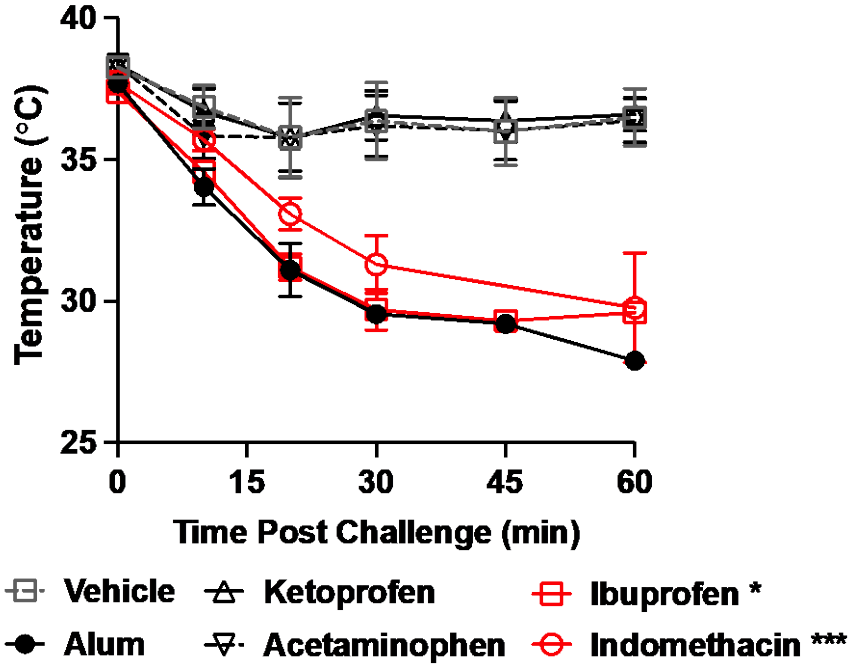
Content current as of:
08/25/2022

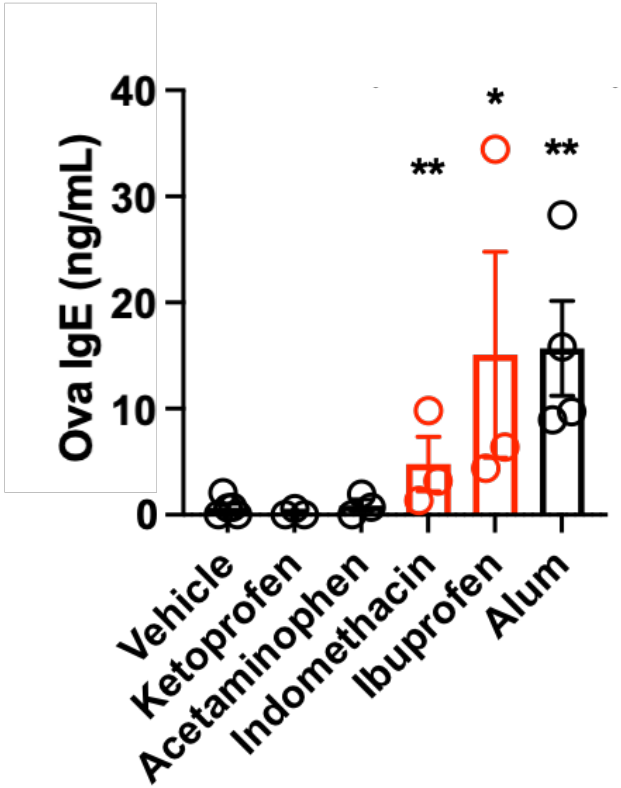
Regulated Product(s)
Food & Beverages
Food & Color Additives

The Screen


OVA
+
Compound
OVA
+
Compound
Day 0
Day 7
Day 14
Sensitization
to OVA?

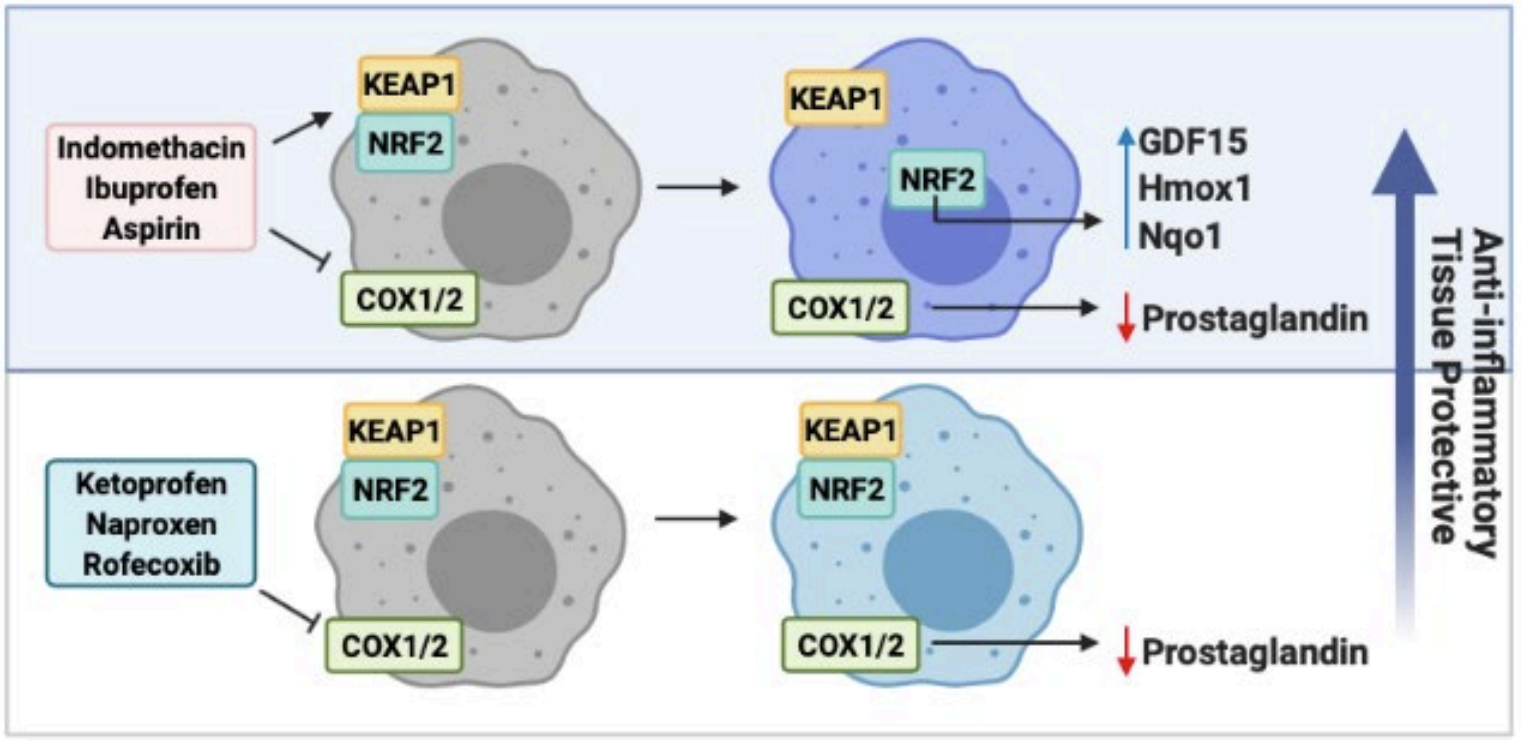
Some NSAIDs are sufficient for allergic sensitization





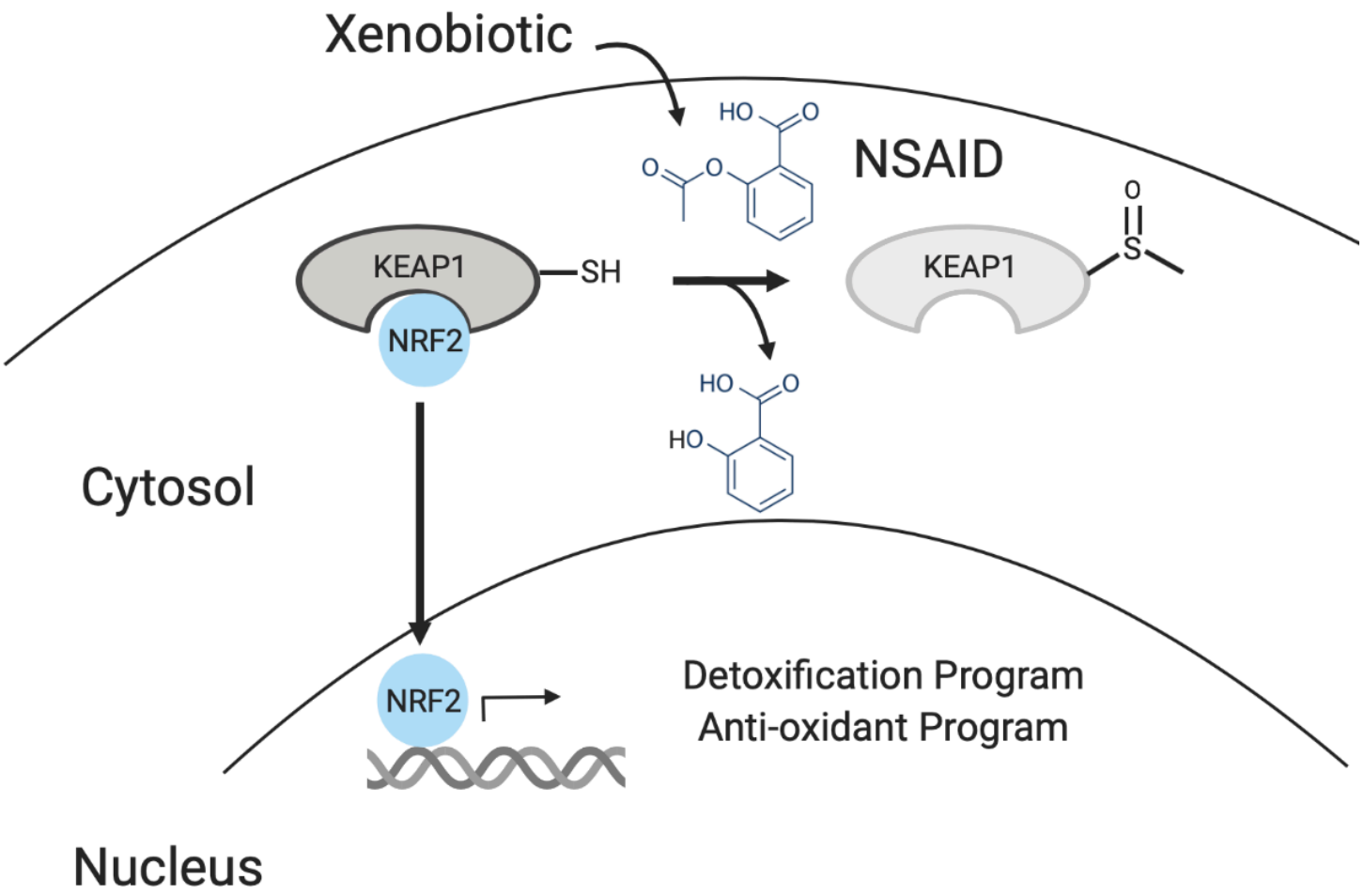
Luan, Hilliard et al. Cell. 2019
Eisenstein, Hilliard et al. Immunity. 2022.
Eisenstein et al. *In Revision.*

A subset of NSAIDs also activate xenobiotic defense pathways

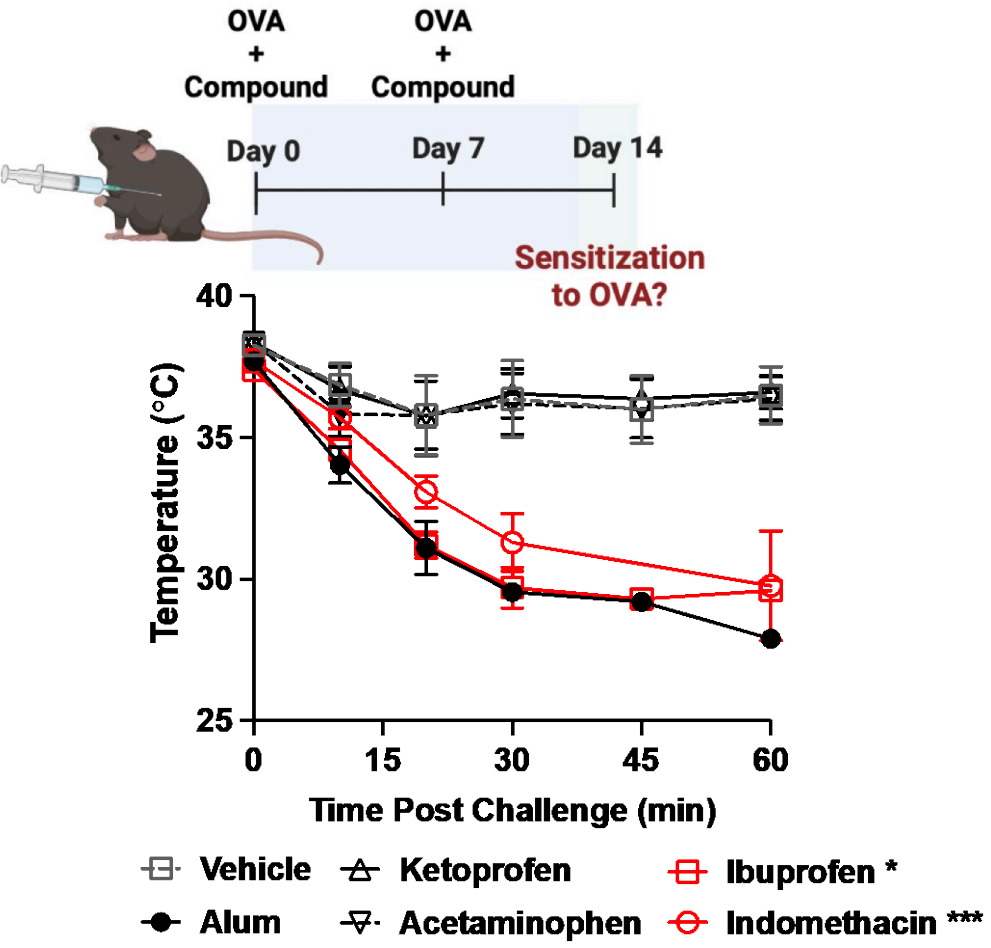


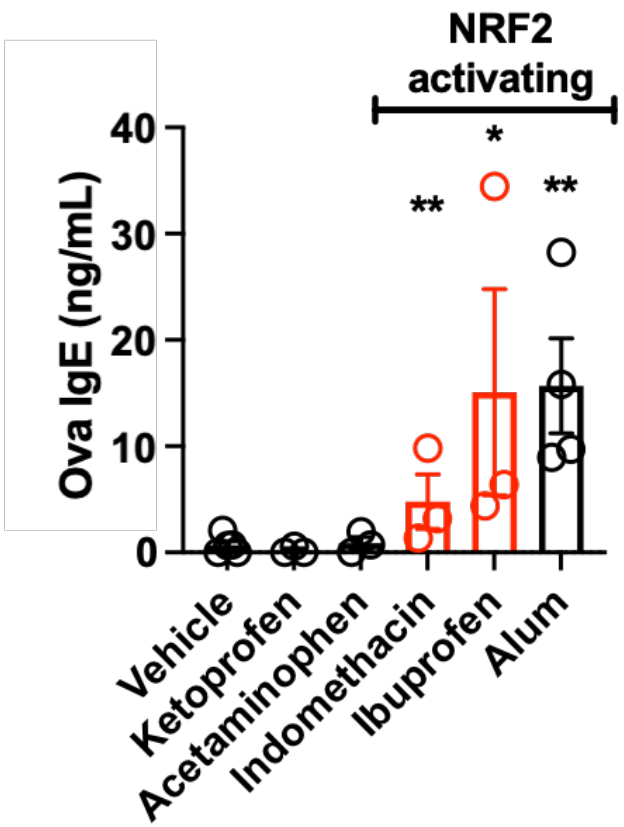
Eisenstein, Hilliard et al. Immunity. 2022.

NRF2/KEAP1 defends against excess electrophiles



NRF2-activatings NSAIDs are allergic adjuvants

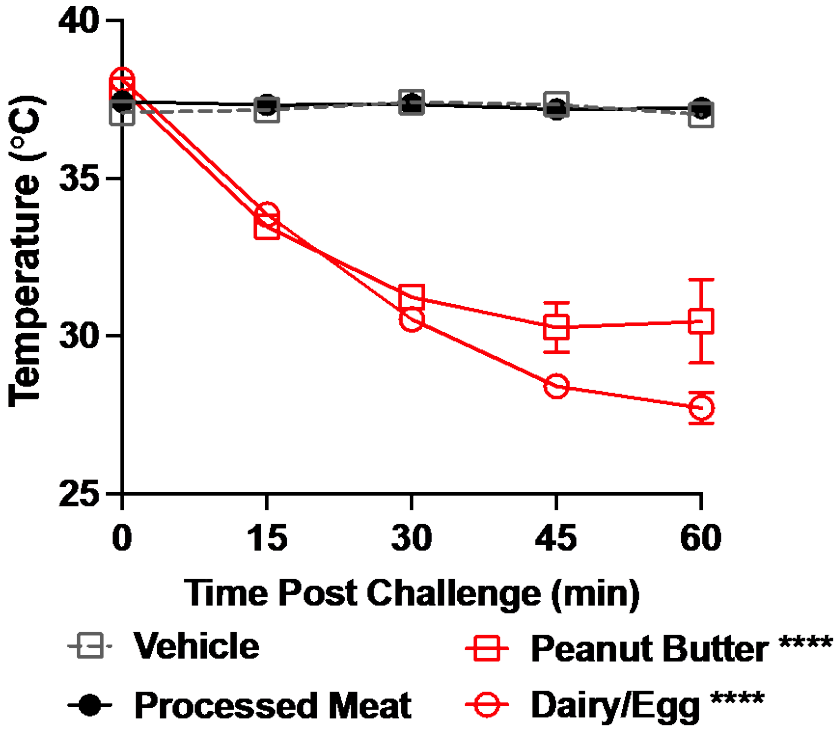




Luan, Hilliard et al. Cell. 2019
Eisenstein, Hilliard et al. Immunity. 2022.
Eisenstein et al. *In Revision.*

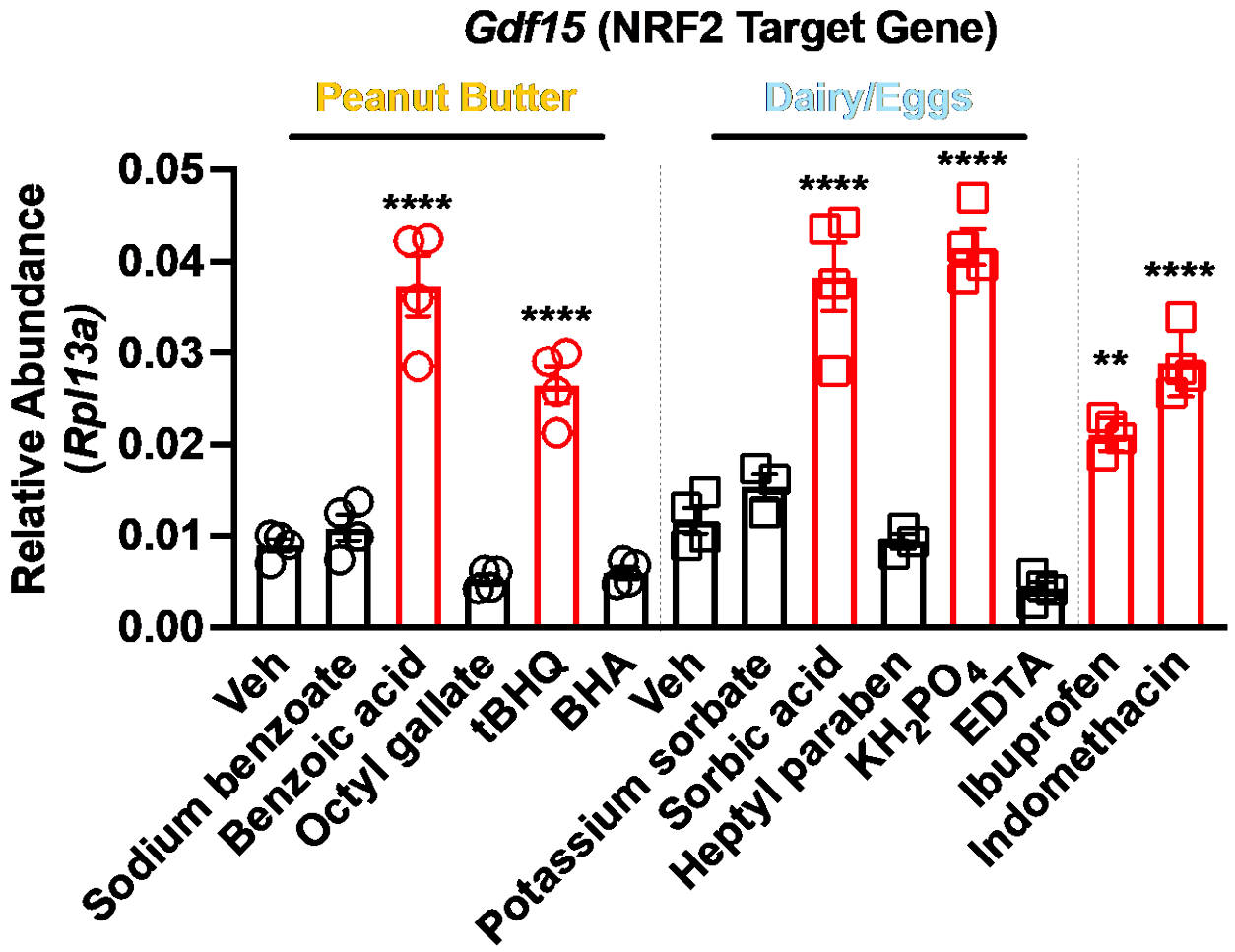
Identification of food additives that are sufficient as allergic adjuvants

Food	Additive
Peanut Butter	Sodium Benzoate, Benzoic Acid Octyl Gallate, tBHQ. Butylated Hydroxyanisole
Dairy/Egg	Potassium Sorbate, Sorbic Acid, Heptyl Paraben, Potassium Phosphate Ethylene Diamine Tetra acetic Acid
Processed Meat	Lignosulfonic Acid Calcium Salt, Sodium Nitrite, Potassium Nitrate, Sodium Nitrate



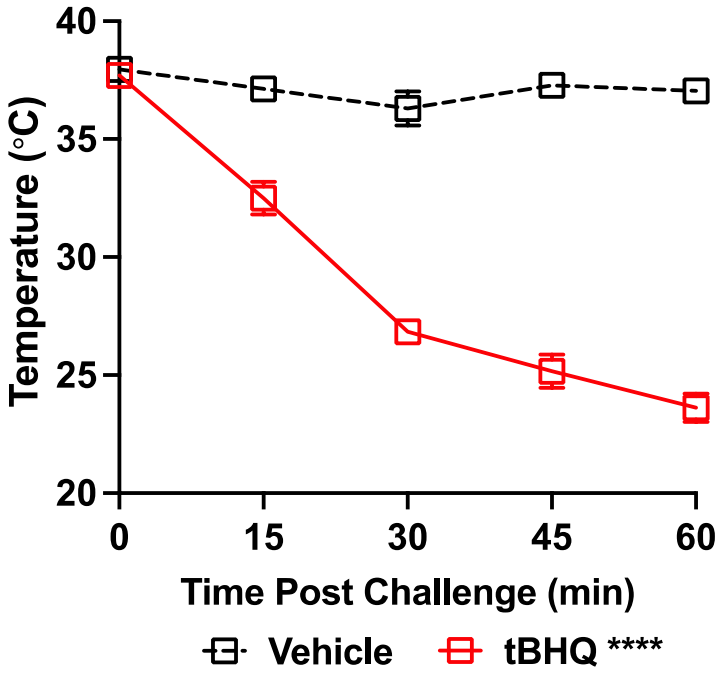
Eisenstein et al. *In Revision.*

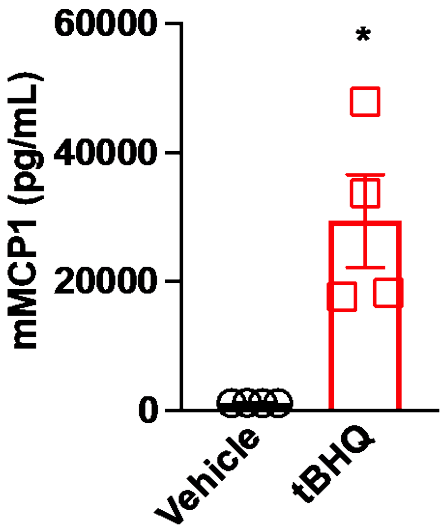
In vitro screen of NRF2 activators identify known and novel activators

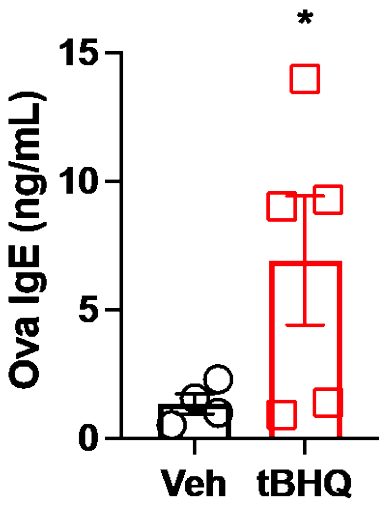


Eisenstein et al. *In Revision.*

The NRF2 activator tBHQ is sufficient as an allergic adjuvant

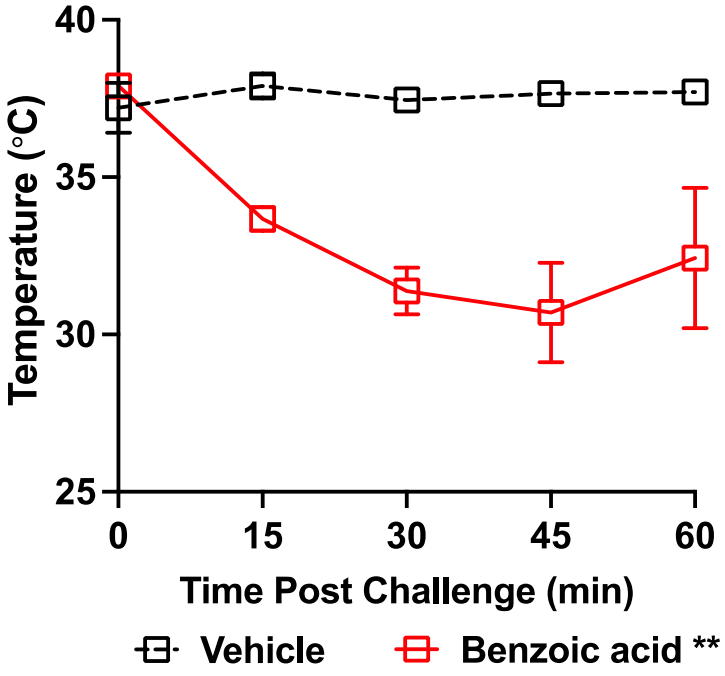


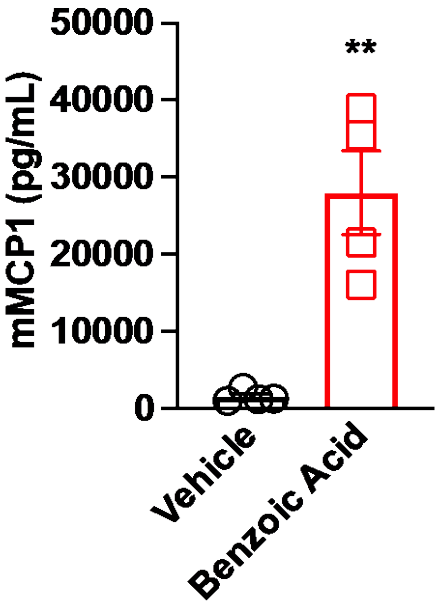


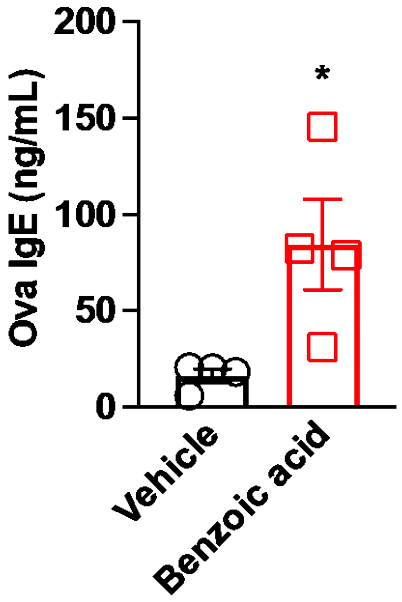


Eisenstein et al. *In Revision.*

Benzoic acid (novel NRF2 activator) is an allergic adjuvant

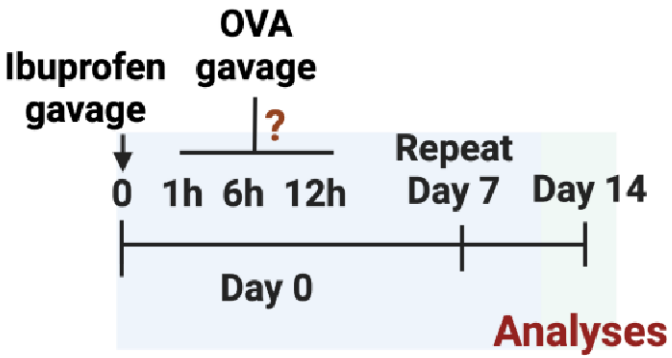


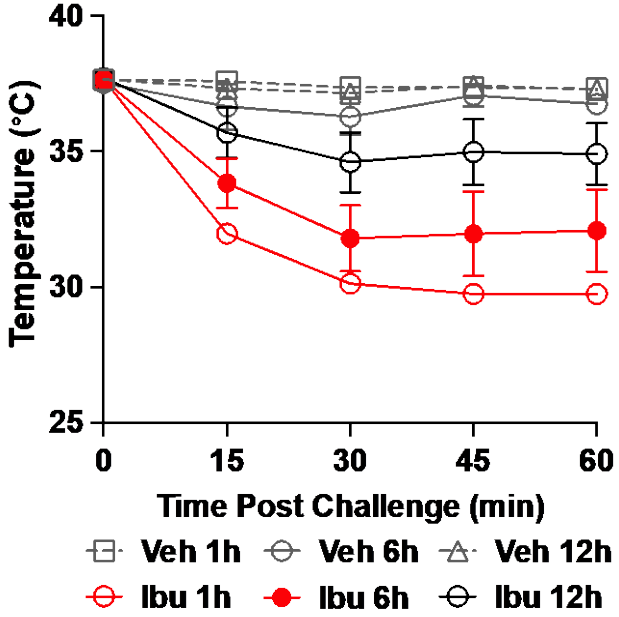


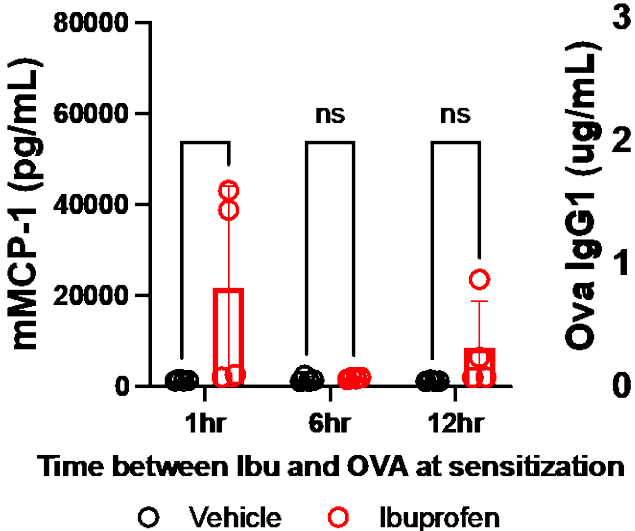


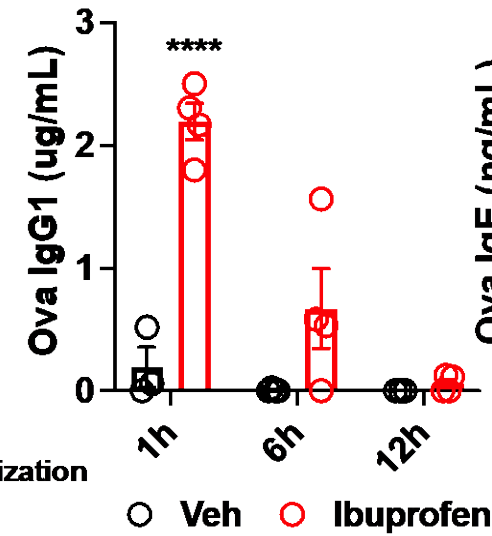
Eisenstein et al. *In Revision.*

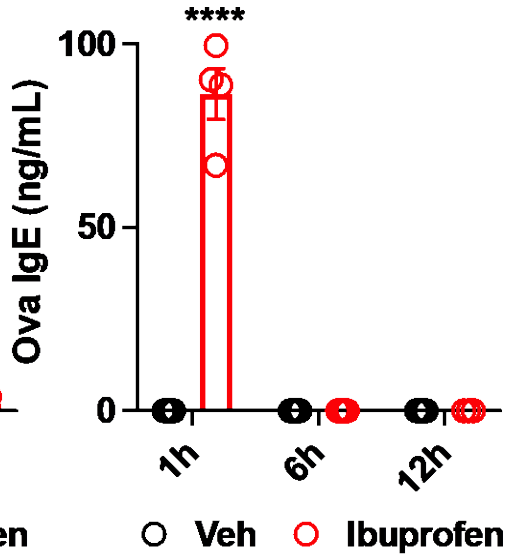
Immune memory formation requires temporal proximity



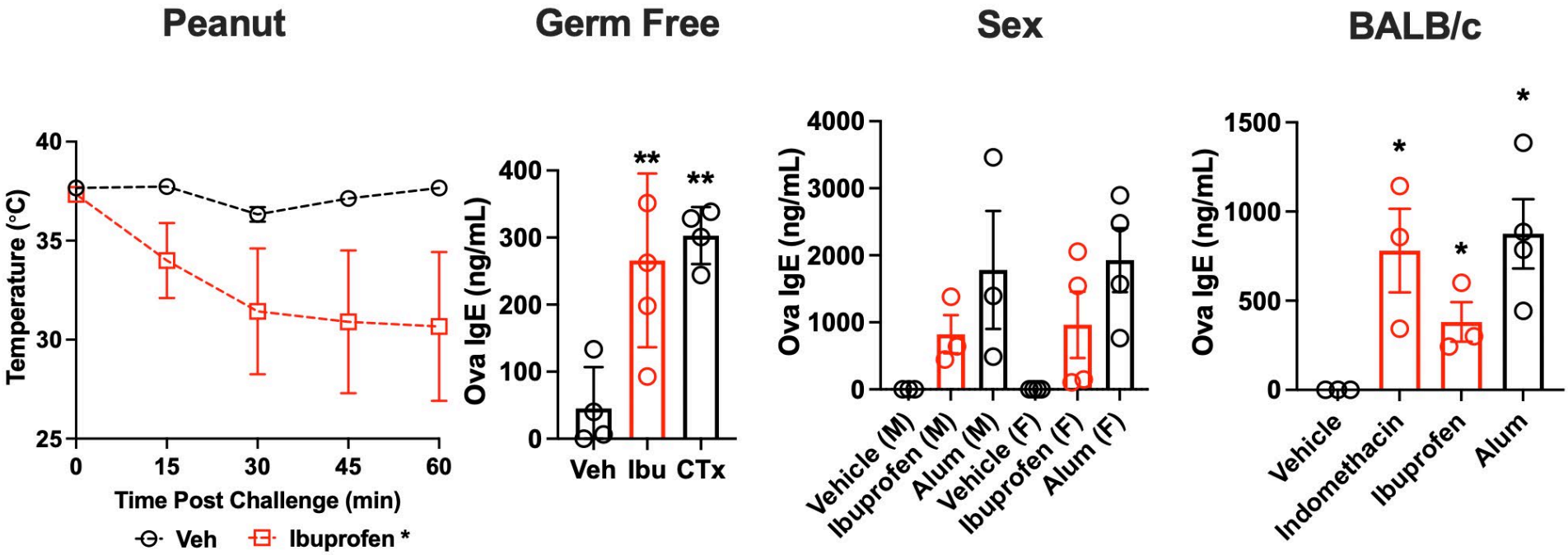






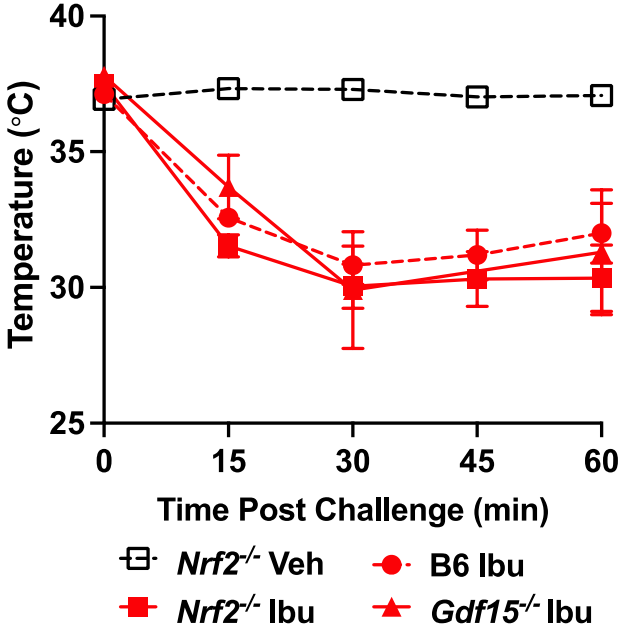


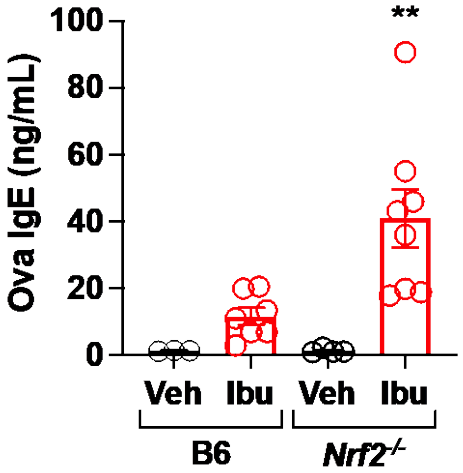
Sensitization occurs with other antigens, independent of microbiome, sex, genotype

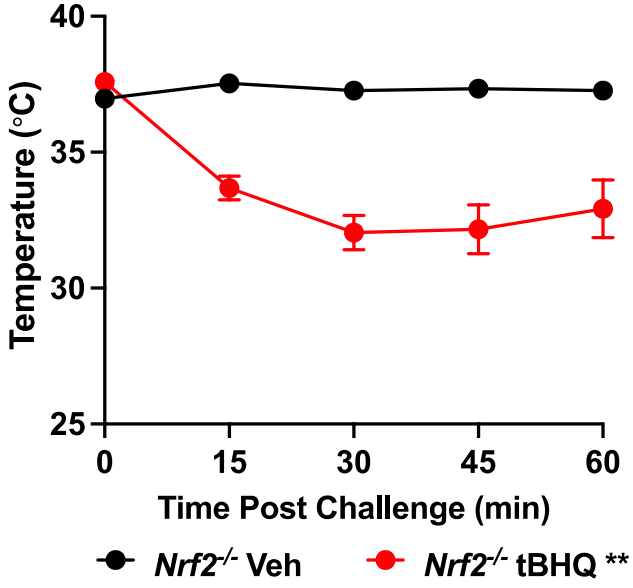


Eisenstein et al. *In Revision.*

How: The NRF2 activators are sufficient, but not necessary, but make things worse…







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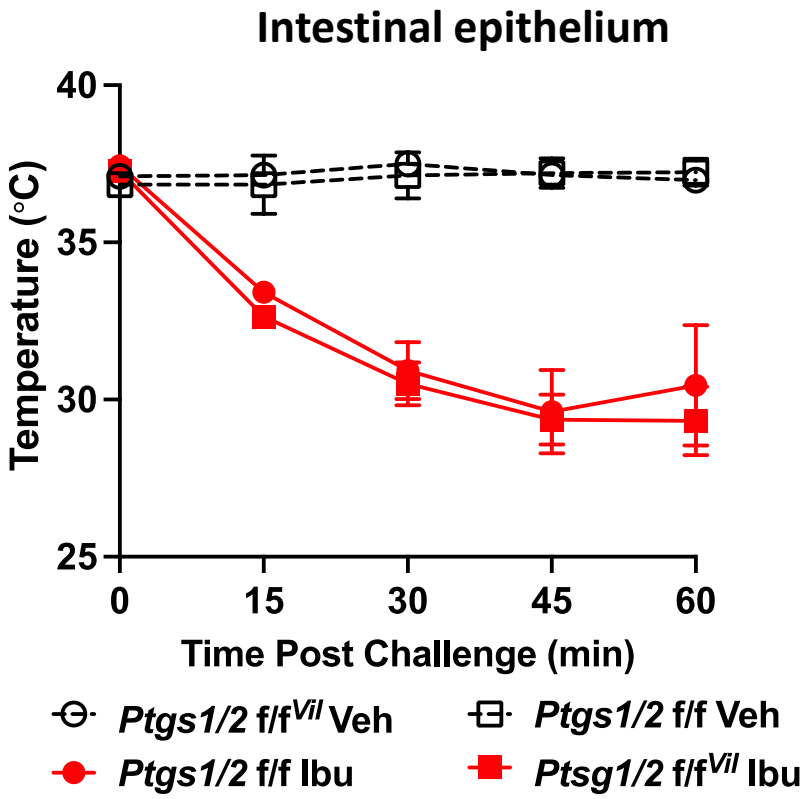
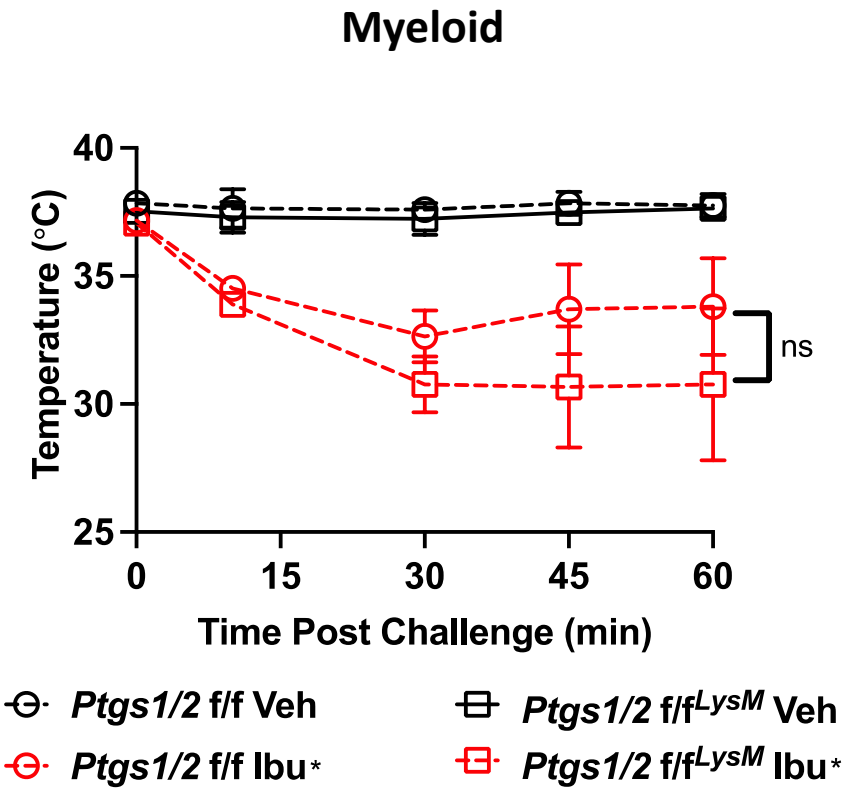
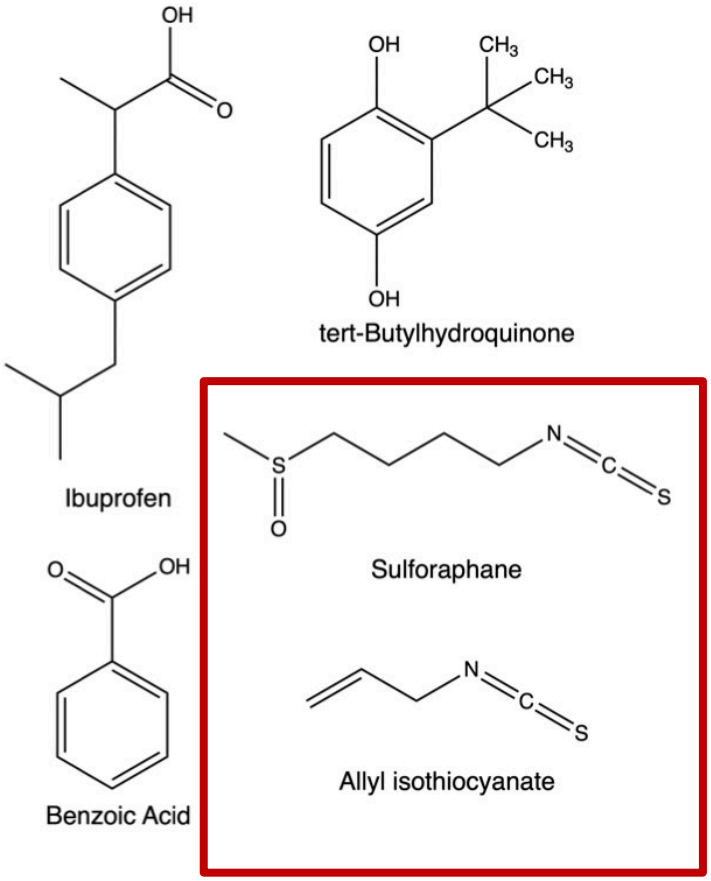
COX isozymes aren't necessary either…





Eisenstein et al. *In Revision.*

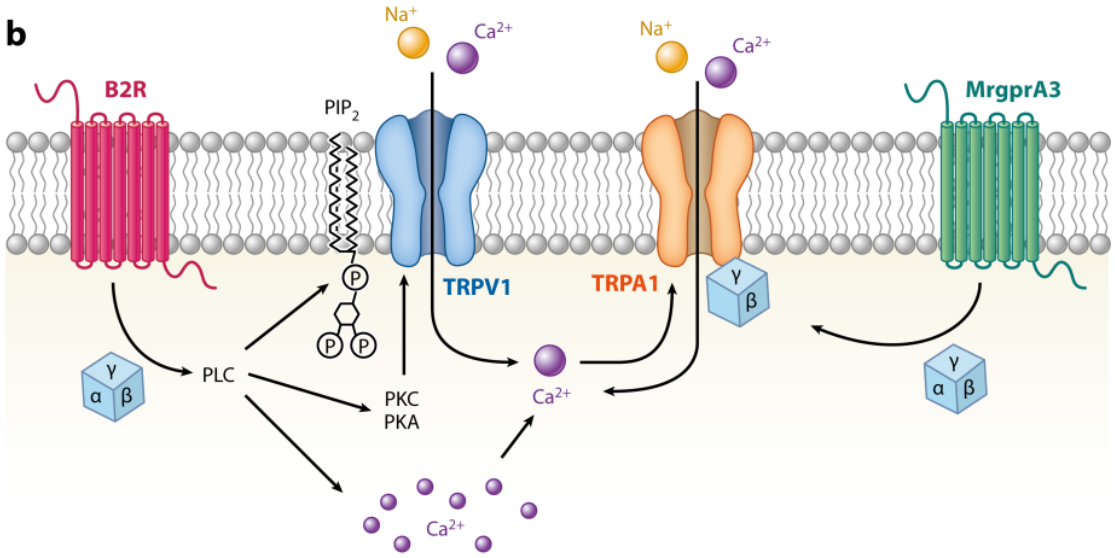
Back to the drawing board looking for the sensor

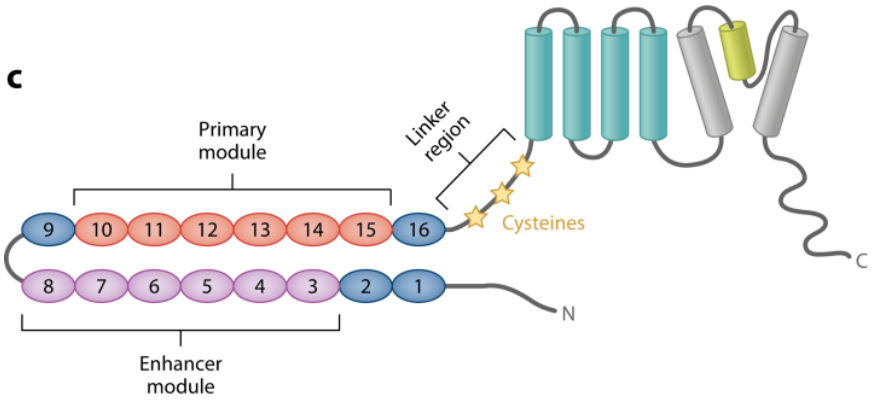


All cytosolic proteins with reactive thiols

Thioredoxin (Trx)
Peroxiredoxins (Prxs)
Protein tyrosine phosphatases (PTPs)
Kelch-like ECH-associated protein 1 (Keap1)/NF-E2-related factor 2 (Nrf2)
Cysteine-rich proteins (CRPs)
Redox-sensitive Ras family proteins (Rho, Ras, Rap)
Redox-sensitive protein kinases (c-Src, PKC)
Redox-sensitive phosphatases (PTEN, PTP1B)
Redox-sensitive calcium release channels (ryanodine receptors)
Redox-sensitive apoptotic proteins (Bcl-2 family proteins)
Redox-sensitive ribonucleotide reductases (RNR)
Redox-sensitive G protein-coupled receptors (GPCRs)
Redox-sensitive ion channels (cysteine-modified potassium channels)
Glutaredoxins (Grxs)
Protein disulfide isomerases (PDIs)
Transient receptor potential channels (TRPA1, TRPM2, TRPM7)
5' AMP-activated protein kinase (AMPK)

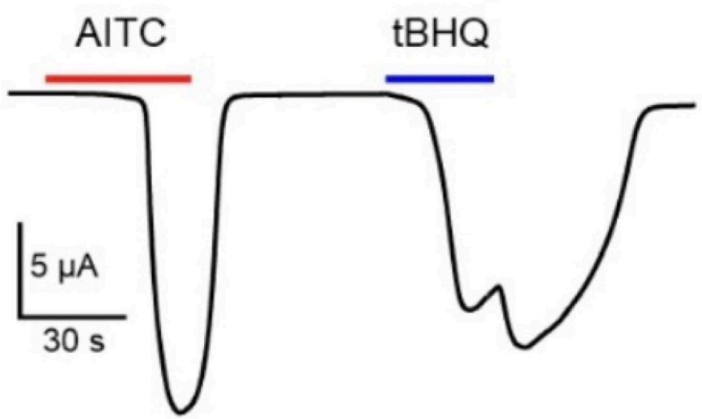
TRPA1: Irritant sensor through thiol sensing

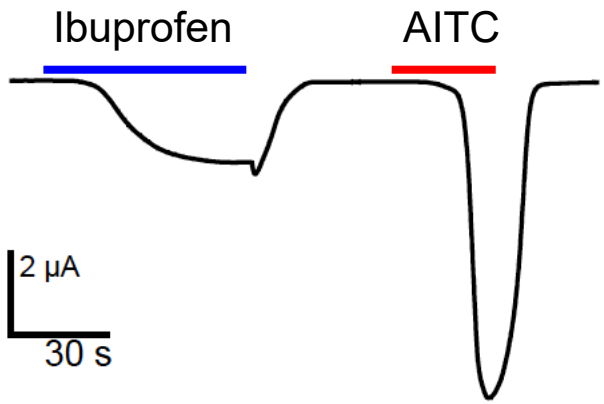




Julius D. 2013.
Annu. Rev. Cell Dev. Biol. 29:355–84

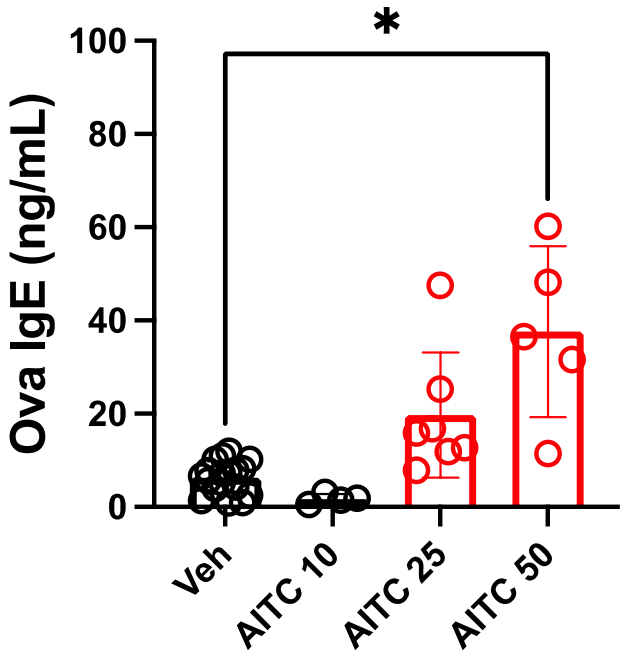
NRF2 activators are TRPA1 activators (electrophiles and reactive cysteins)

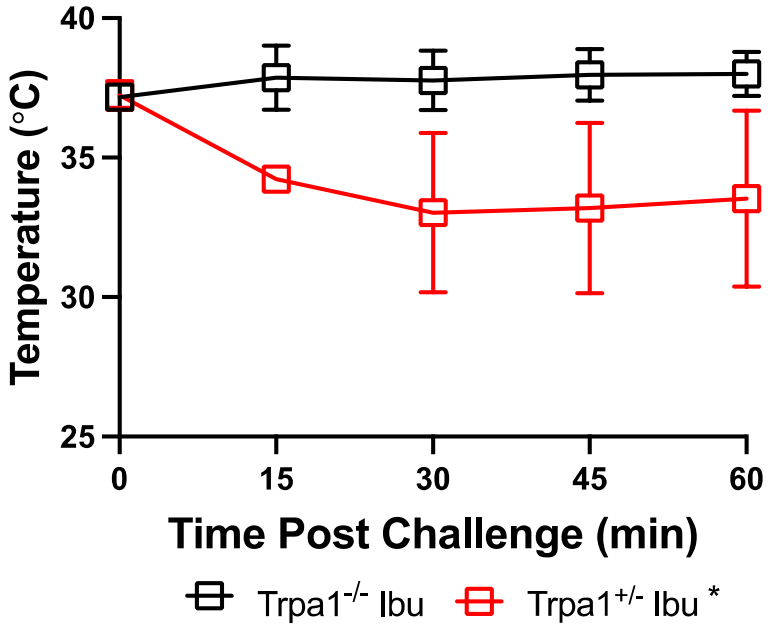




Eisenstein et al. *In Revision.*
With Gracheva Lab

TRPA1 is necessary and sufficient for xenobiotic sensitization

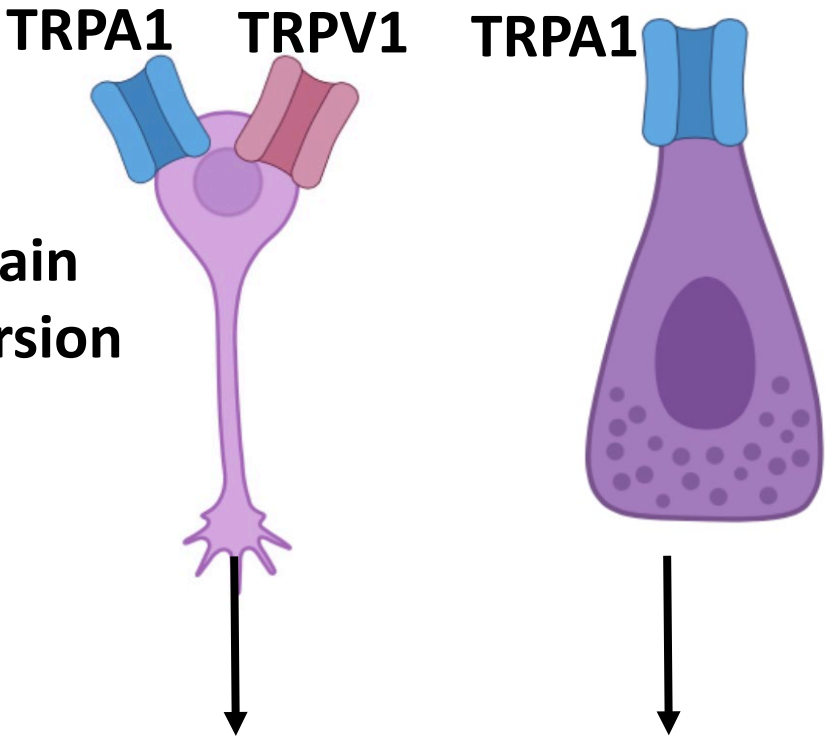




Eisenstein et al. *In Revision.*

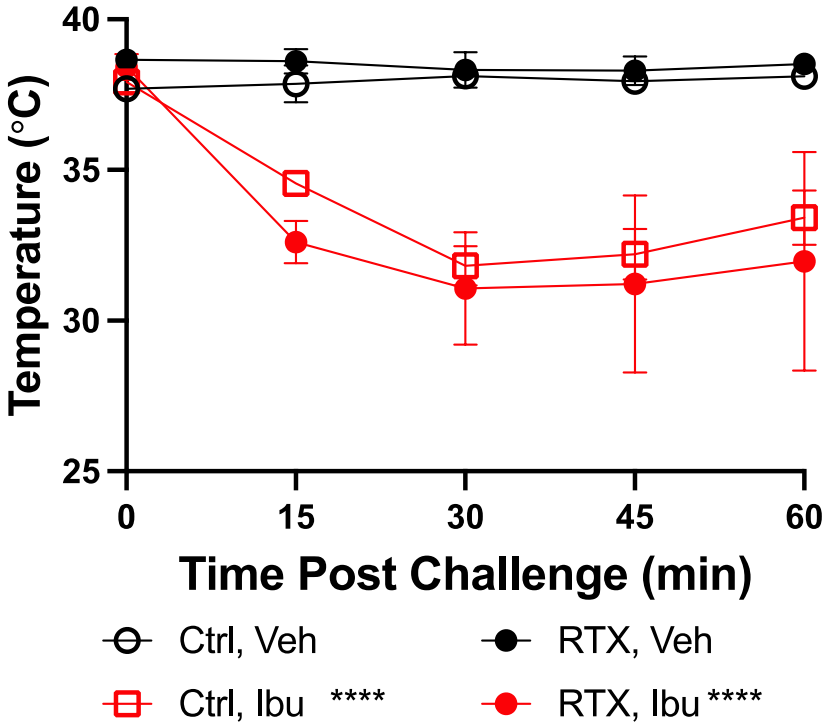
TRPA1 is expressed on neurons and enteroendocrine cells

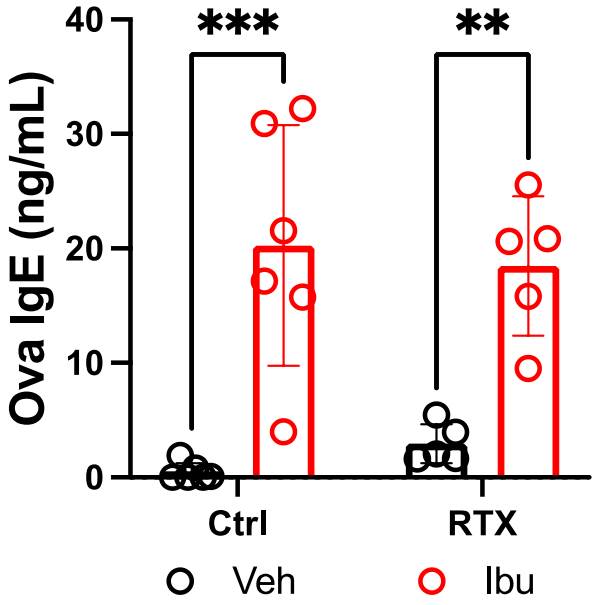
Mediate:
Itch
“Wasabi” burn/pain
Noxious cold aversion



Mediate:
- Mucus production
- Increased intestinal motility
- Increased tight junctions

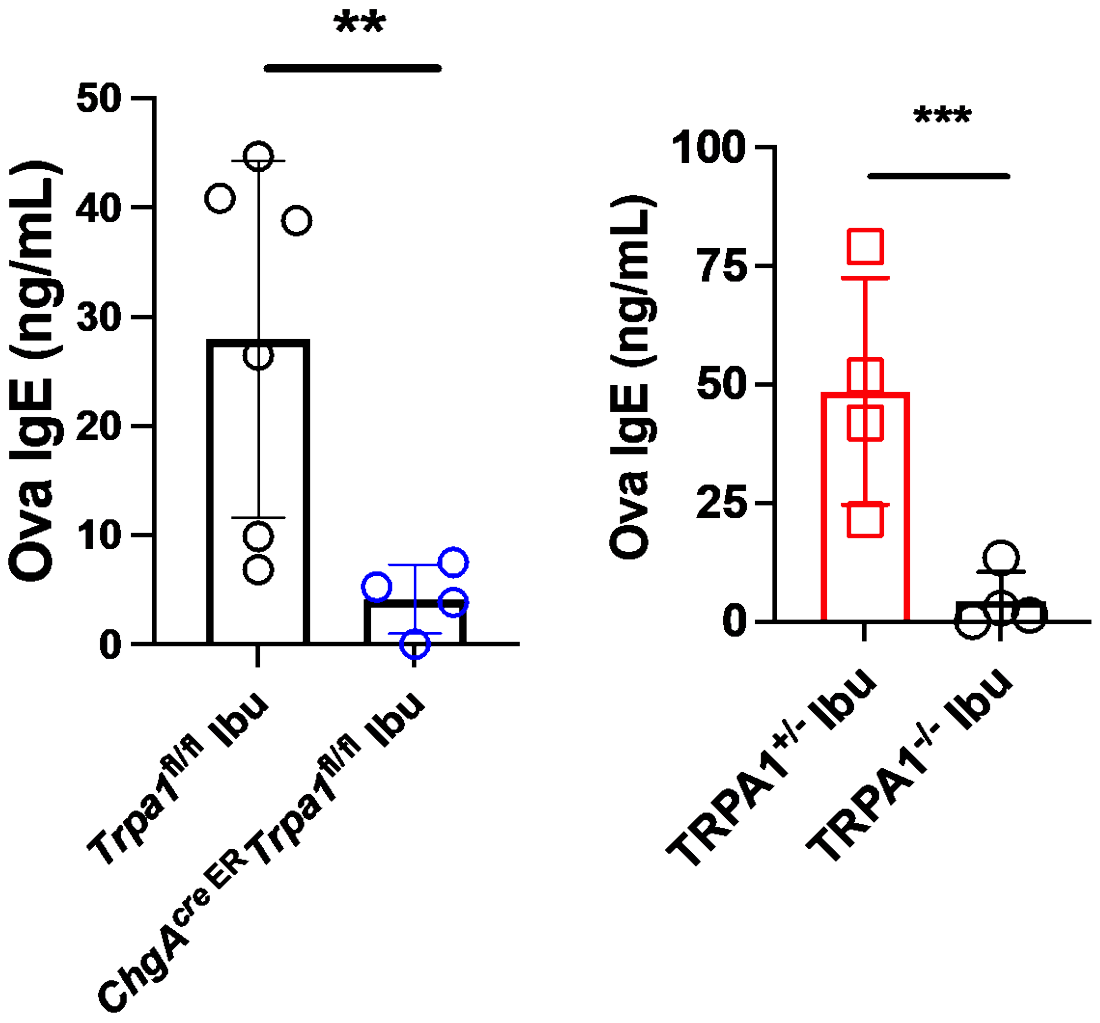
Neuronal TRPA1 (via TRPV1 deletion) is dispensable





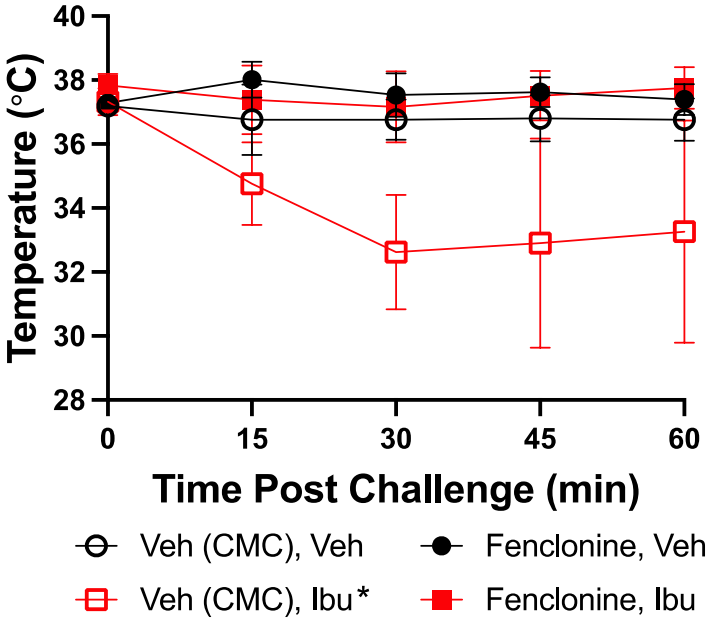
Eisenstein et al. *In Revision.*

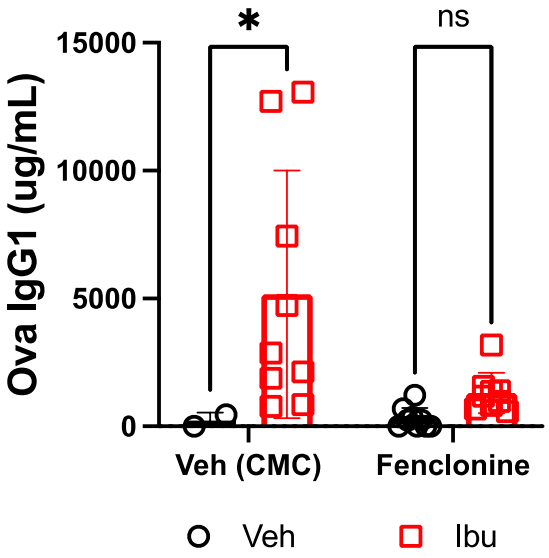
EEC deletion of TRPA1 phenocopies whole body knockout

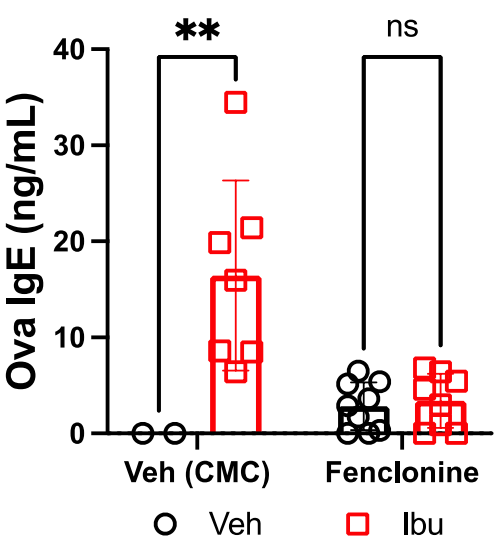


Eisenstein et al. *In Revision.*
With Wu lab (NIH)

Serotonin is required for sensitization

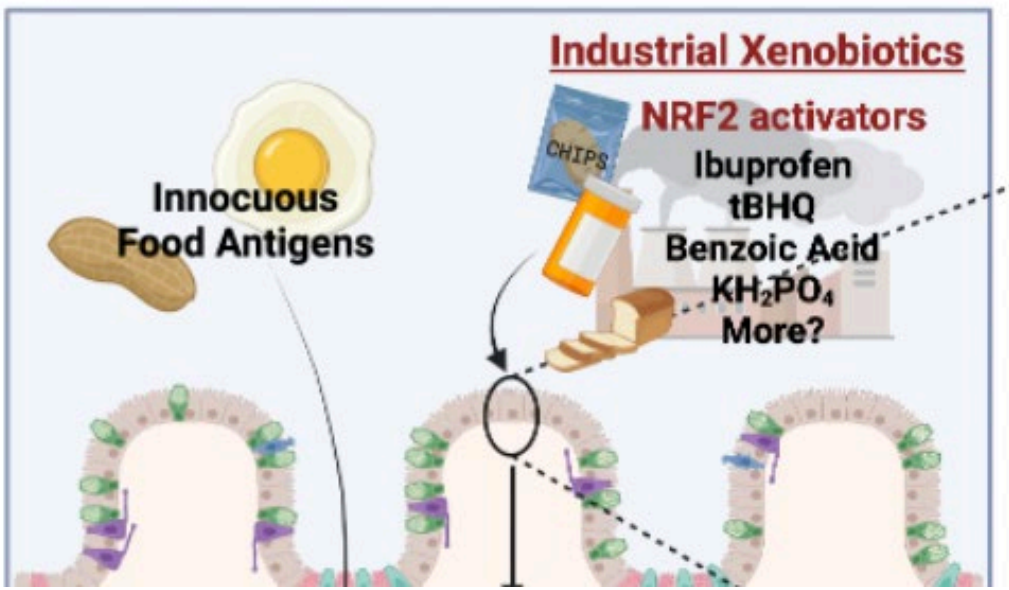


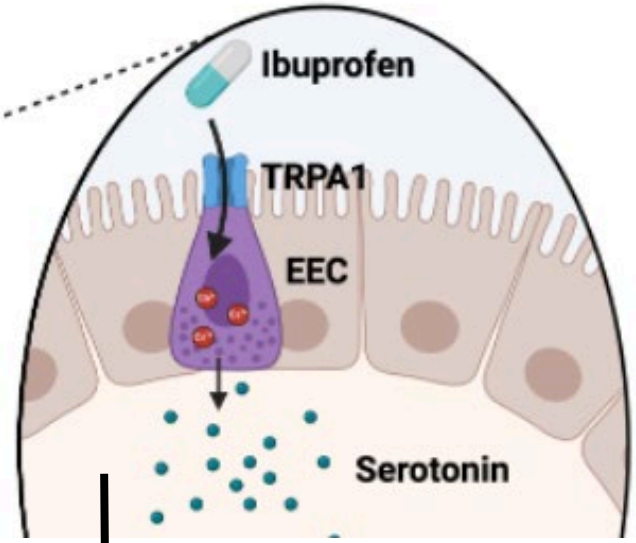




Eisenstein et al. *In Revision.*
With Wu lab (NIH)

Summary Part I





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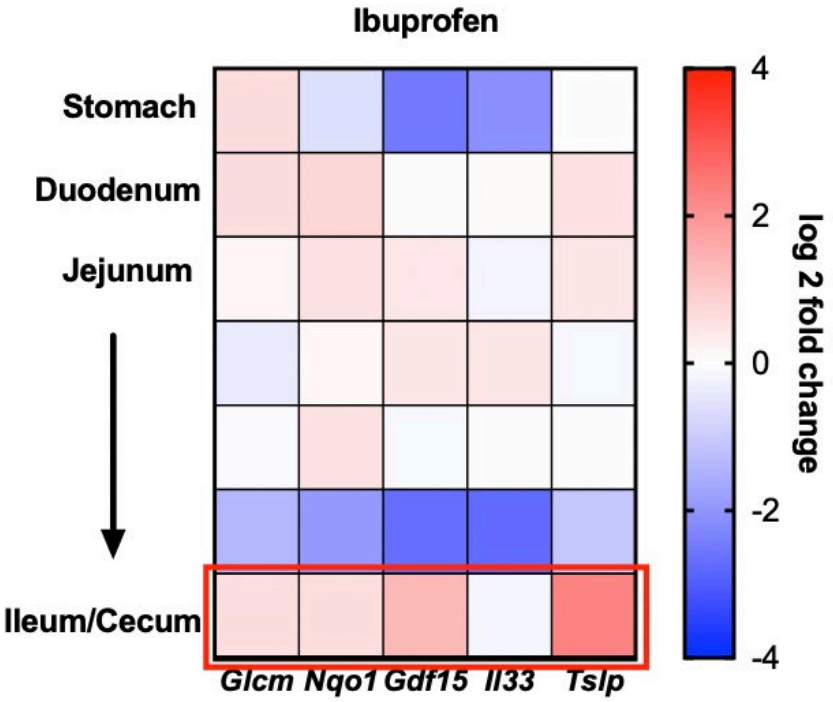
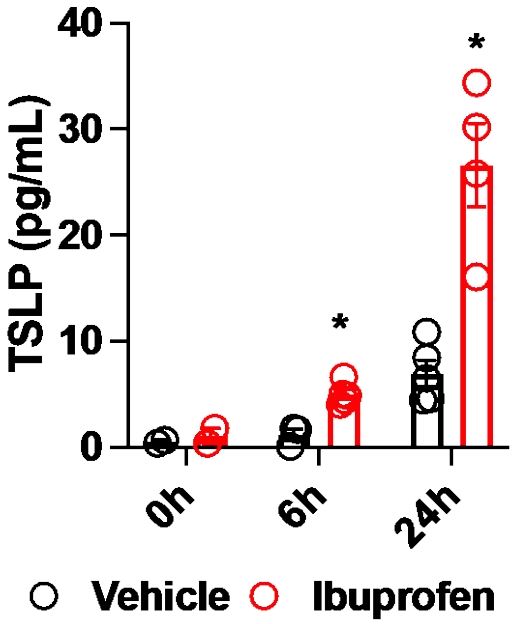
Sensitization

Eisenstein et al. *In Revision.*

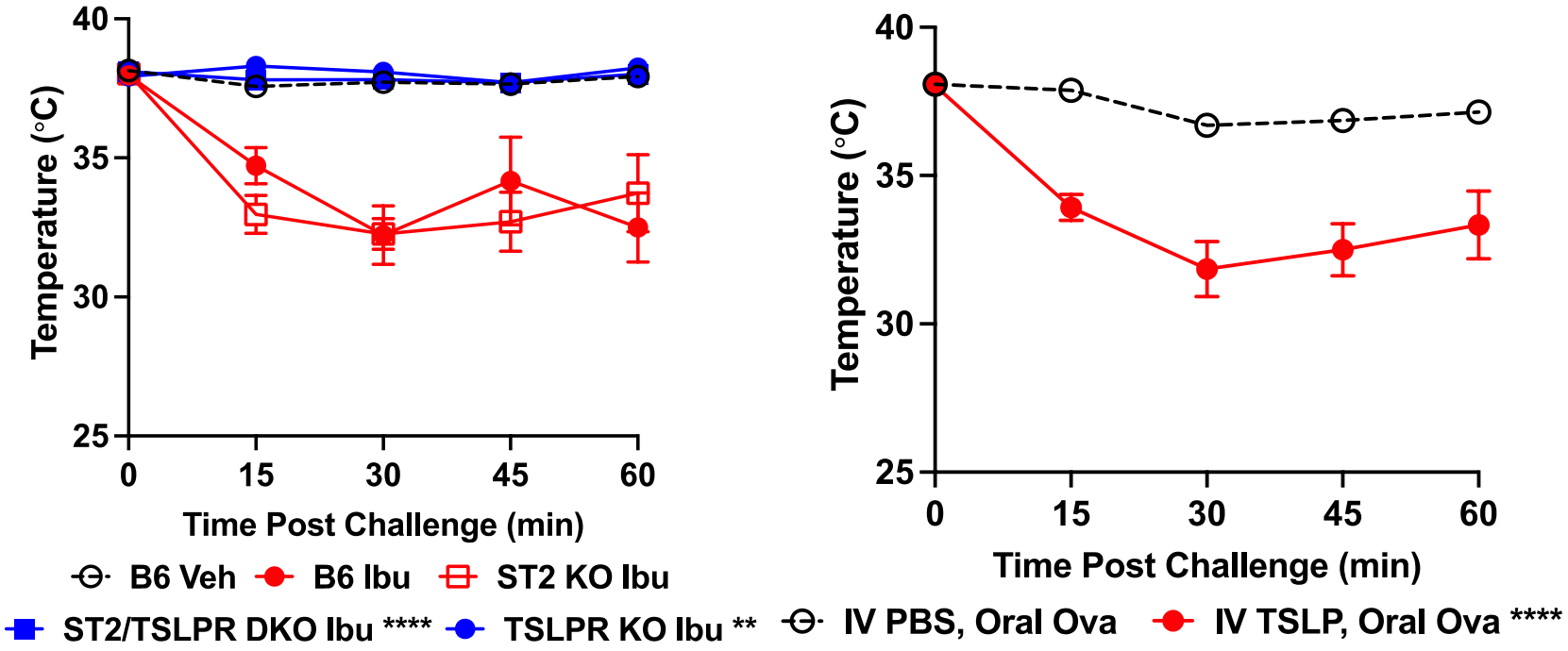
Where? Ibuprofen induces NRF2 program and alarmins in the ileum





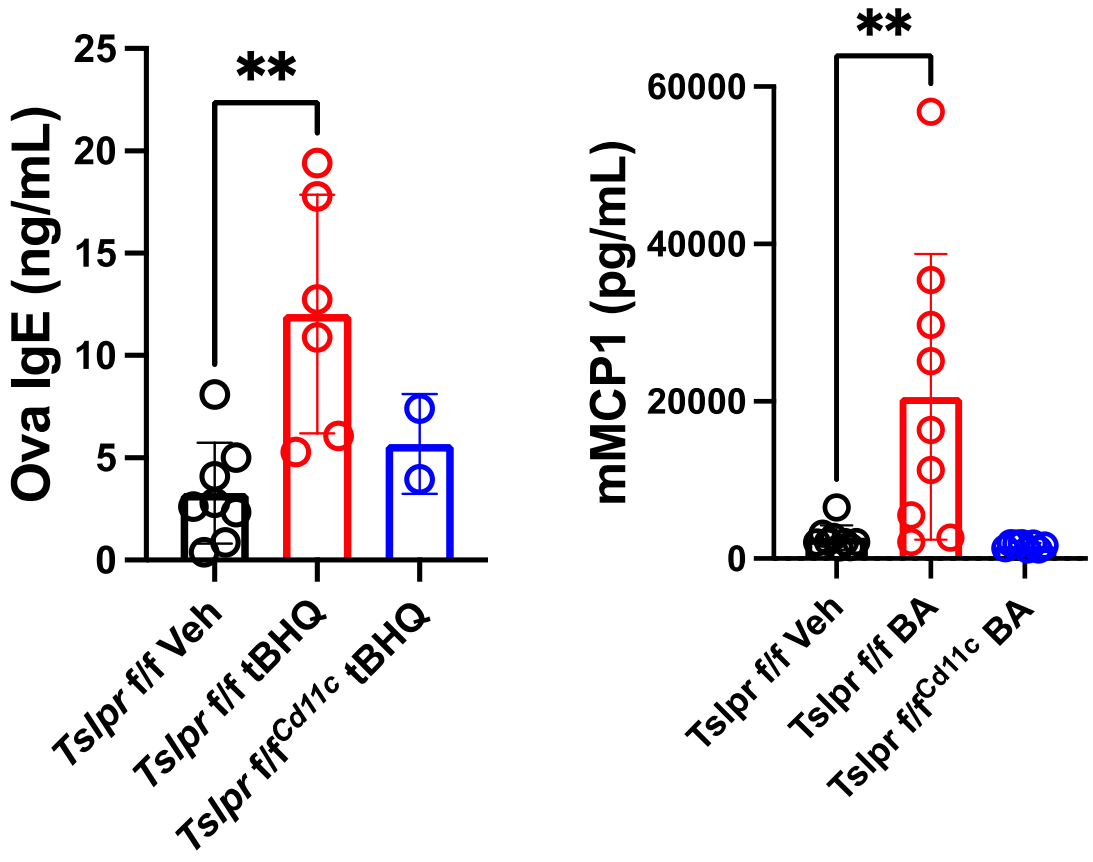
Eisenstein et al. *In Revision.*

TSLP is necessary and sufficient for xenobiotic sensitization



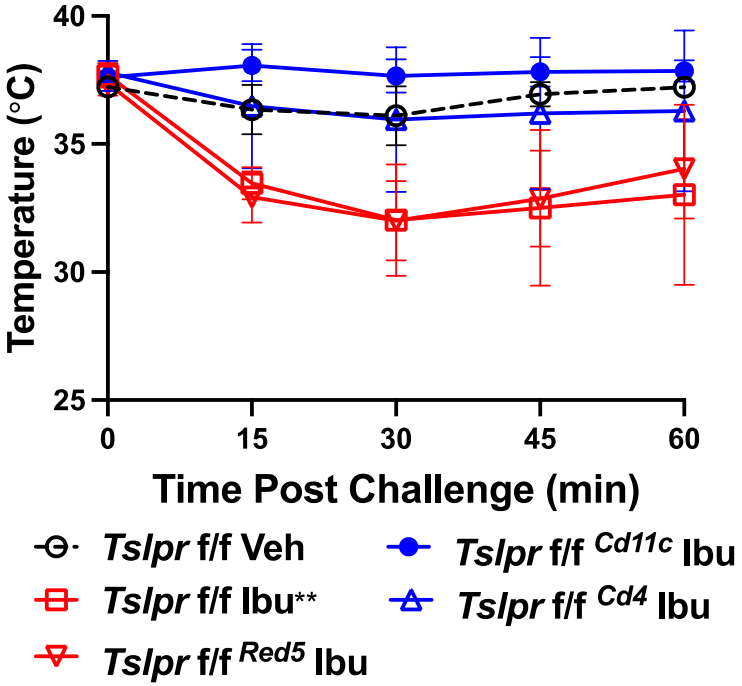
Eisenstein et al. *In Revision*.
Waizman et al. *In Revision.*
Gift of Rich Locksley (UCSF)

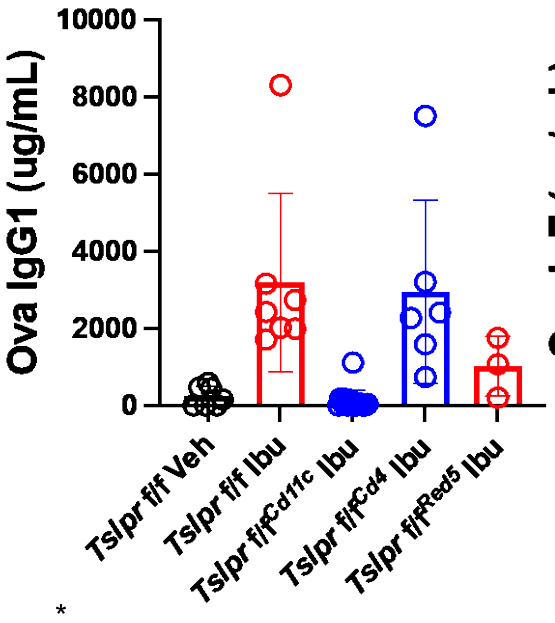
TSLP is necessary and sufficient for xenobiotic sensitization (generally)

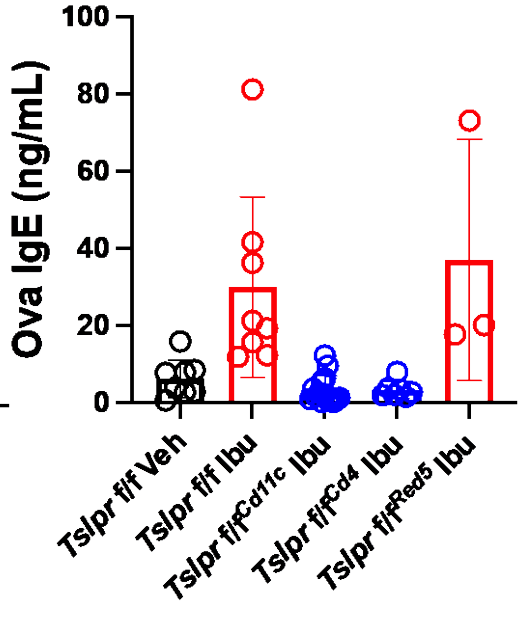


Eisenstein et al. *In Revision*.
Gift of Rich Locksley (UCSF)

TSLP signals on dendritic cells and CD4 T cells to direct allergic memory

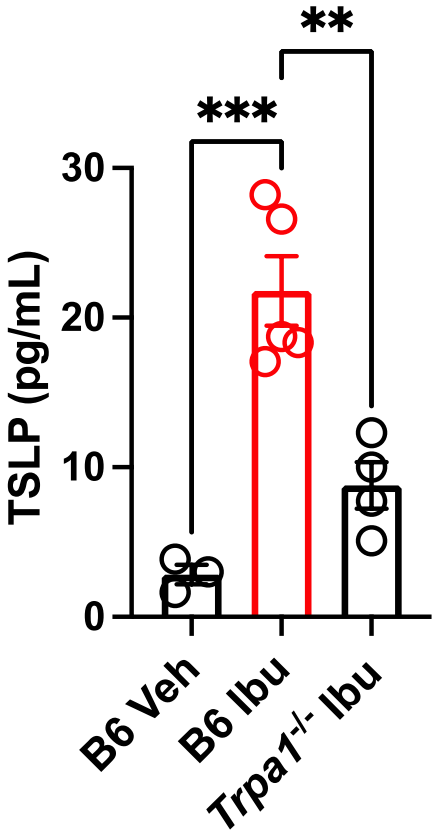


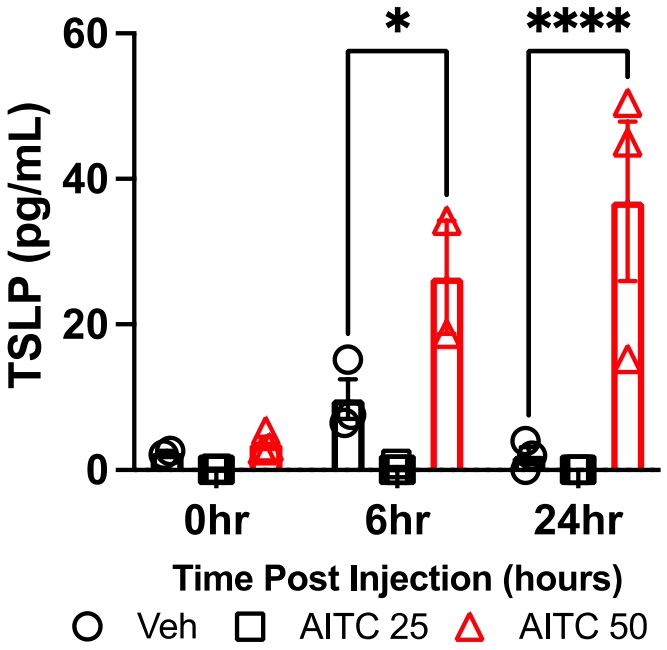


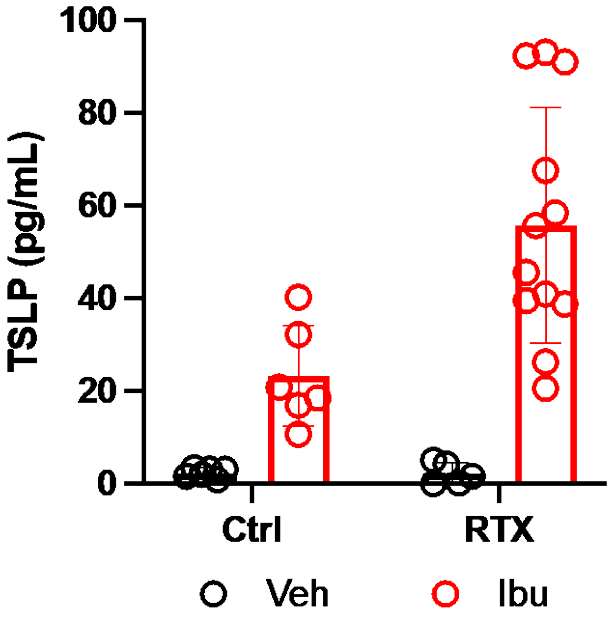


Eisenstein et al. *In Revision*.
Gift of Steven Ziegler (Benaroya)

TRPA1 is necessary and sufficient for TSLP induction

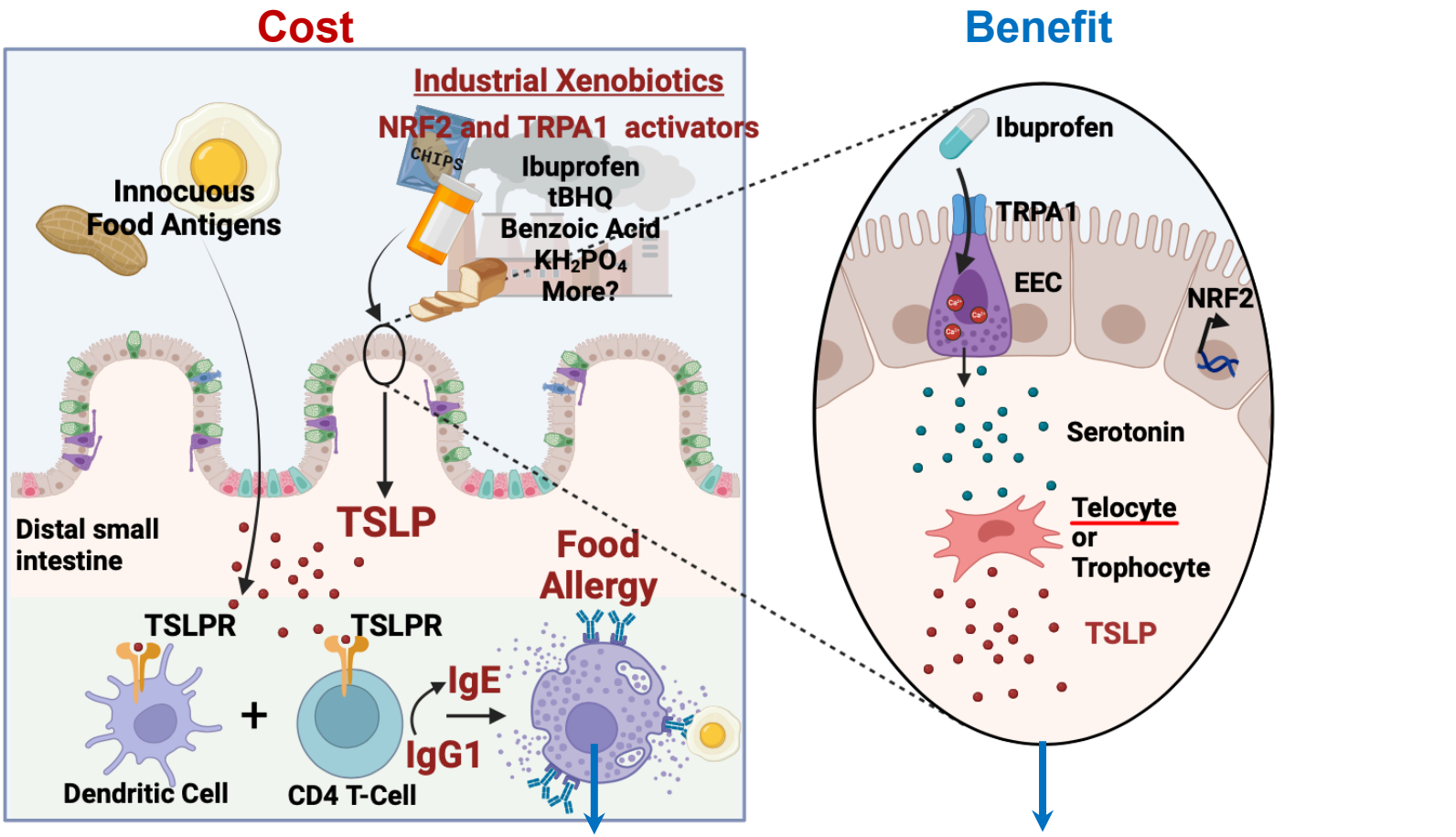






Eisenstein et al. *In Revision.*

Identification of food additives that are sufficient as allergic adjuvants



Eisenstein et al. *In Revision.*

How about in people? NSAID use is associated with anaphylaxis in claims data

Medicaid data 1990-2015 CA and FL

	Non-NSAID User (%)	NSAID User (%)	P value
Total Cohort	8,849,067	24,198	
Asthmatics	595,238 (6.7)	3,062 (12.6)	<0.001
Acute asthma exacerbation	171,740 (1.9)	777 (3.2)	<0.001
Anaphylaxis	5,680 (0.06)	34 (0.14)	<0.001
Allergy	67,301 (0.8)	198 (0.8)	0.315
Atopic Dermatitis	10,767 (0.1)	35 (0.1)	0.352

Eisenstein et al. *In Revision.*
With Abbas Shojaee

Case control survey study at Yale

Environmental Exposures in the Development of Food Allergies



Does your child have food allergies or eczema?

Would you like to contribute to our understanding of the development of food allergies?

What does participation in the study involve?

Completion of a confidential online questionnaire that asks questions about your child's food allergies or eczema and about products used by the child in infancy.

You will receive $50 gift card for completion of the survey.

Follow the link or scan the QR code to access the survey:

https://yalesurvey.ca1.qualtrics.com/jfe/form/SV_9mMtCmkDLAwM3Vs

Yale IRB 2000034319

Questions: Anna Eisenstein, MD PhD, Assistant Professor of Dermatology, anna.eisenstein@yale.edu, Phone: 203-500-3918

Eisenstein et al. *In Revision.*
With Gary Soffer

Case control survey study at Yale: Interim Analyses

	Odds Ratio	95% Confidence Intervals	n	P value
Atopic Dermatitis	5.07	1.98-12.95	86	0.0007
Fever/pain medication use	2.14	0.88 – 5.23	82	0.094
Exposure to store-bought food	0.70	0.25-1.95	78	0.487
Exposure to formula	1.16	0.38-3.50	84	0.790

Open Question

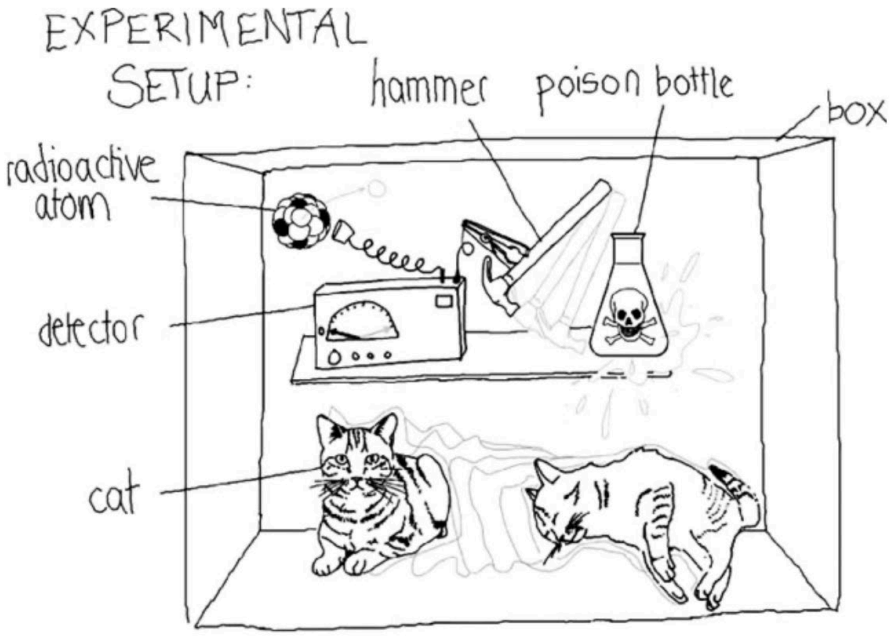
Pattern Recognition Receptors **TRPA1/NRF2, others?**

Type I	Type II
Complete Freund's Adjuvant	Aluminum salts (Alum)
LPS	Cholera Toxin
Squalene	Chitin
Flagellin	Papain
Poly(I:C)	Plant lectins
Lipid A analogues – MPL, RC529, GLA	Ara h 1
Imiquimod	Bioactive lipids
Emulsions (MF59)	

Open Questions

If the "environment" matters, what in it, exactly, matters?

Are disease trajectory divergences random or knowable?



E. Schrôdinger. Naturwissenschaften. 1935
Schleich et al. Applied Physics B. 2016.

Lab

Mentorship: Ruslan Medzhitov, Joe Craft, Ward Wakeland
Mike Brown, Mike Carroll

Family and Farm