6th ANNUAL Functional Pharmacy Symposium

FUNCTIONAL MEDICINE Continuing Education

Understanding the Long-Term Implications of COVID as the Progenitor of Chronic Inflammatory Diseases

Andrew Heyman, MD MHSA

Ritchie Shoemaker, MD

FUNCTIONAL MEDICINE Continuing Education

Disclosures

- CMO Metabolic Code

Objective

- Identify the potential of a SARS-CoV-2 infection to trigger chronic autoimmune diseases.

Shoemaker R, et al. *Medical Research Archives* vol 9 issue 7. Medical Research Archives

RESEARCH ARTICLE

Treatable metabolic and inflammatory abnormalities in Post COVID Syndrome (PCS) define the transcriptomic basis for persistent symptoms: Lessons from CIRS

Authors

Shoemaker R[1], McMahon S[2], Heyman A[3], Lark D[4], van der Westhuizen M[5], Ryan J[6].

CHRONIC INFLAMMATORY RESPONSE SYNDROME (CIRS)

- NAMED SINCE 2010
- ROBUST PUBLISHED LITERATURE OVER 25 YEARS
- NO ROLE FOR MYCOTOXINS IN URINE
- NO ROLE FOR ANTIFUNGALS
- INCREDIBLY COMMON; RX HAS ROBUST LITERATURE
- PROTOCOLS LET DOCS COMPARE NOTES ACROSS THE GLOBE

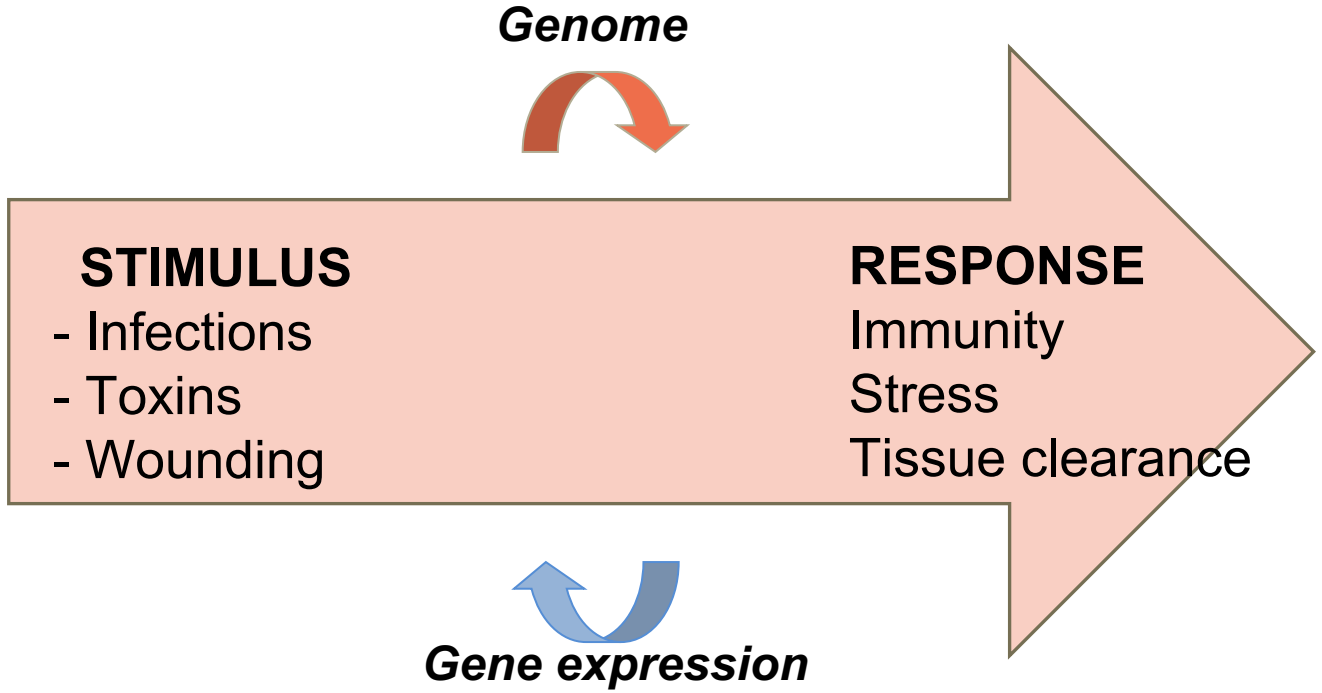
Biotoxin symptoms clusters

- Fatigue, weak
- Headache
- Aches, cramps
- Unusual, sharp, claw, electrical
- Light sens, redness, blurring, tearing
- SOB, cough, sinus
- Abdominal pains, secretory diarrhea

- Joints, AM stiff
- Exec. cognitive memory concentration. Word assimilation, confusion, disorientation
- Mood, appetite, sweats, temp regulation
- Thirst, pee, shocks
- Numbness, tingling, taste
- Vertigo, tremor, skin

Functional Genomics:

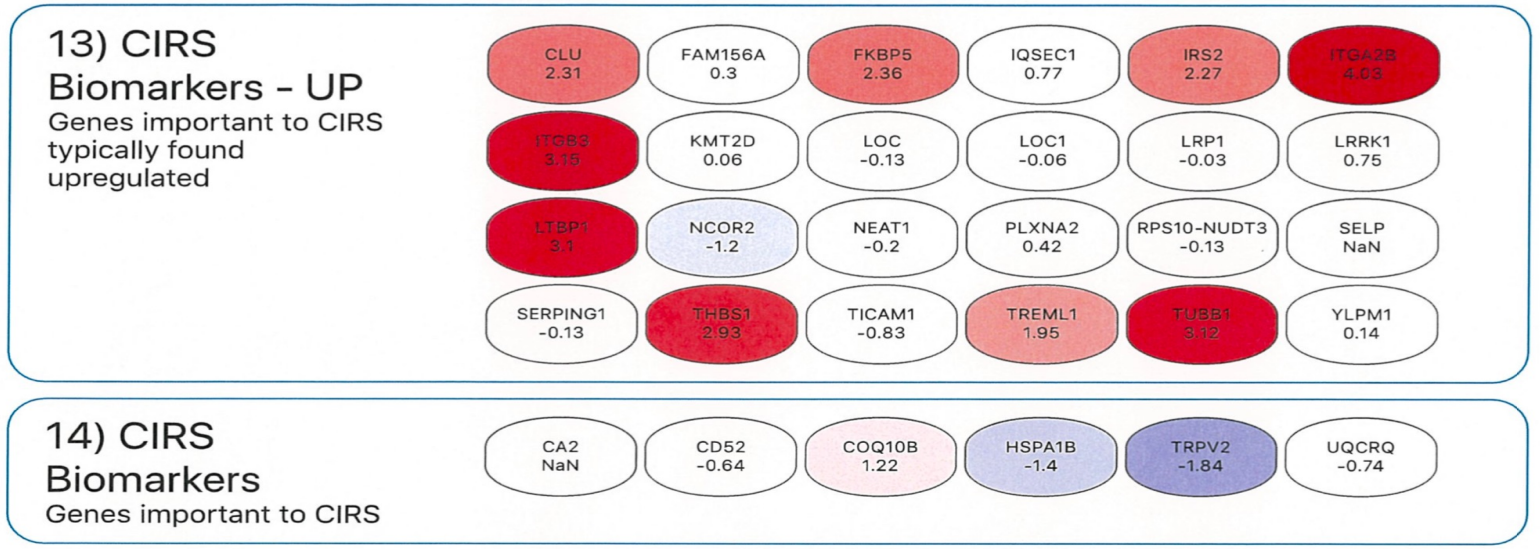
Why do Patients Become Stuck?



- Monitor transcriptomic activity using RNA-Seq
  - ***Transcriptome*** = set of all RNA molecules produced by the genome at any one time

❖ **transcriptomes are sensitive indicators of both disease status and emerging health hazards**

CIRS biomarkers by stage



Stage	EI4G21	NEAT1	NCOR2	TREML	VIPR1
1	1	6	13	7	1
2	6	8	8	8	2
3	3	0	3	2	4
4	1	0	5	3	2

MOLECULAR HYPOMETABOLISM NAMED IN 2016 BY DR. JAMES RYAN

- REDUCTION OF RNA FOR LARGE AND SMALL RIBOSOMAL
- MITORIBOSOMES TOO
- AND THE NUCLEAR-ENCODED MITOCHONDRIAL GENES
- TRANSLOCASES, THE FERRY BOATS FOR MITOCHONDRIA
- ATP SYNTHASES IN THE MATRIX
- ELECTRON TRANSPORT CHAINS ALSO IN THE MATRIX

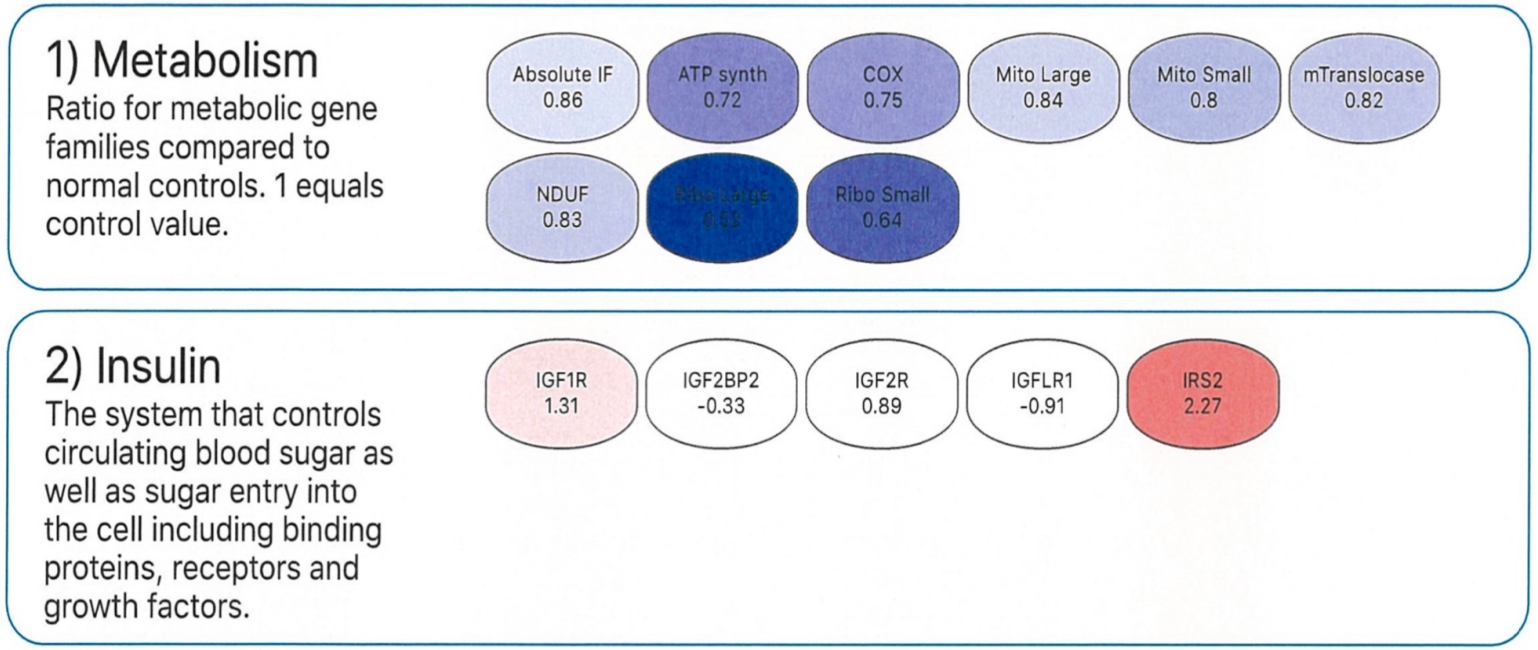
What is proliferative physiology

- Cell signals say, ”make more” raw materials
  - Then divide. Microtubules become key
- Assuming available supply of building blocks for new cells and energy; glycolysis “side shoots” is key
- Part of prolif physiology is a result of processes that will divert resources to make cells rapidly
- But if the cell is a T reg or a neuron needing Na+ gradients; or if the cell is part of RV or pulmonary vasculature, really bad things will follow

SO, COMBINING MHM AND PROLIF PHYSIOLOGY MEANS

- ONGOING FATIGUE, WEAKNESS AND RESPIRATORY SYMPTOMS
- COGNITVE DYSFUNCTION WARNING OF BRAIN INJURY
- FIBROSIS RISK! CLOTTING RISK!
- LOW VO2 MAX; PULMONARY HYPERTENSION
- ACHE, CRAMP-GET THE PICTURE?
- MULTISYSTEM, MULTI-SYMPTOM ILLNESS CALLED CIRS
- 20+ BIOMARKERS SAY **TESTS ARE ABNORMAL**
-

MHM/+IRS2



- Compared to control data sets, we see a group of patients here with a correlation of MHM/+IRS2 with worsening end organ injury in untreated, Stage 1 CIRS patients.
- A widened anion gap, consistent with metabolic acidosis.
- An increased percentage of cases in this group with atrophic grey matter nuclei or enlarged superior lateral ventricle enlargement as shown by NeuroQuant.
- PAH is far more common in this group compared to MHM +/ (-) IRS2; MHM (-) / (-) IRS2; and MHM (-) / +IRS2.

This table for Stage 1 (untreated) has the basis of CIRS in 4 columns

	MHM+/IRS2+	MHM+/IRS2-	MHM-/IRS2-	MHM-/IRS2+
N=	62	26	16	8
ATRO NUC/6	4.1	3.0	2.8	1.2
% SLV UP	16.1	7.6	6.1	0
Mean IRS2	1.78	-0.97	-1.67	1.14
% Anion gap > 12	85	20	33*	0
% PASP increase	80	8	0	0

LET'S CHECK IN WITH POST COVID-19

- LOOKS LIKE CIRS
- ACTS LIKE CIRS
- DOES IT HAVE CIRS BIOMARKERS?
- SYMPTOMS YES; PROGRESSIVE; YES? LITTLE SELF-HEALING; YES
- DEVASTATING? CAN BE, YES!
- BUT NOT DEVASTATING FOR EVERYONE!

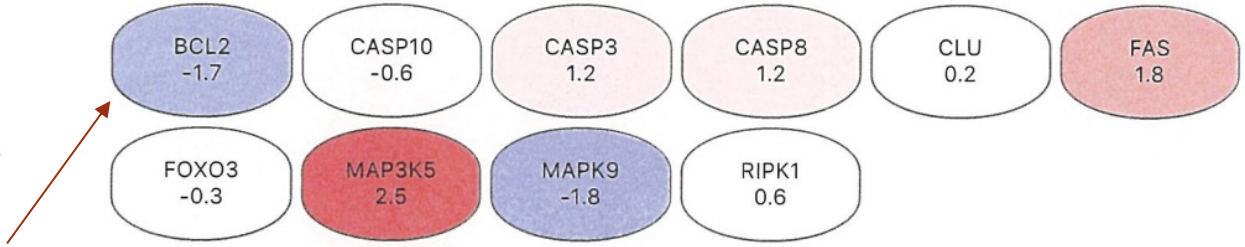
SARS-CoV-2 (COVID-19) COMES FIRST

- OUTCOME RANGES FROM FATALITY TO ASYMPTOMATIC
- NEW SYMPTOMS AFTER COVID
  - PCS (-): NO DISRUPTION OF ADL
  - PCS (+): DISRUPTION OF ADL
- WHAT DETERMINES DIFFERENCES IN OUTCOME
- SYMPTOMS SOUND JUST LIKE CIRS

COVID Long Haulers: Apoptosis

3) Apoptosis

Can be triggered by mild cellular injury and by various factors internal or external to the cell; the damaged cells are then disposed of in an orderly fashion.



Stage	LRP1	CLU	Casp 3	Casp 8	Casp 10
1	15	7	3	3	5
2	9	9	9	2	3
3	1	2	0	1	2
4	1	2	0	1	4

CIRS BIOMARKERS, DO PCS PATIENTS HAVE THEM? SOME DO, SOME DON'T

- VCS
- PROTEOMICS, INFLAMMATION; HORMONAL
- METABOLIC; PROLIFERATIVE PHYSIOLOGY
- PULMONARY HBP; TR $\geq$ 2.5 M/SEC
- VO2 MAX; AGE RELATED; < 25 ML/KG/MIN
- TRANSCRIPTOMICS (HURRAH!)

GENIE CRUCIAL TO INSIGHT

- MOLECULAR HYPOMETABOLISM
- APOPTOSIS/DEFECTIVE APOPTOSIS
- COAGULATION
- TGFBR 1, 2, 3 +/MAPK+ SPECIFIC IMMUNOREACTIVITY IF ACTINOS > 15 SPECIES (newer methods paper)
- CD 14; TLR 4 SPECIFIC IMMUNOREACTIVITY IF ENDOS > 100
- CD3D; CD48 DEFECTIVE AG PRESENTATION

LEST WE FORGET WHAT GENIE DOES

- LYME
- DEFENSINS KEY TO DIFFERENTIAL DIAGNOSIS
- ENVIRONMENTAL SENSITIVITY
- CIRS BIOMARKERS
- PTSD
- TUBULINS

THE OBSERVATIONAL STUDY PROOF OF CONCEPT

- CONCEPT: PCS IS POST VIRAL CIRS
- ENTRY CRITERIA
  - POSITIVE TEST, FOLLOWED BY NEG; VCS DONE ON SM
- 21 PATIENTS ENROLLED
  - 7 PCS (-) AS OUR CASE CONTROLS
- TREATMENT NOT PART OF STUDY
- ENVIRONMENTAL SAMPLING NOT PART OF STUDY

BIOMARKERS SYMPTOMS, VCS, MHM PROLIFERATIVE PHYSIOLOGY

Table 1	SX	VCS + %	MHM %	Prolif Phys %
Controls	2.7	2	0	0
CIRS	22.3	92	85	88
PCS (-)	8.2	0	0	88
PCS (+)	18.2	75	100	79
p-Value	0.013	0.003	<0.0001	<0.0001

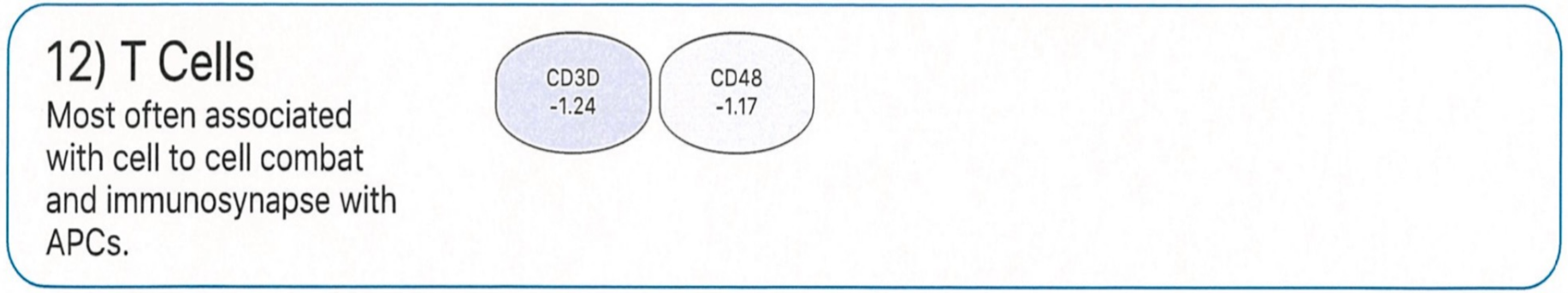
BIOMARKERS APOPTOSIS NECROPTOSIS COAG AND DEFENSINS NOT SO MUCH

Table 2	Apoptosis %	Defective Apoptosis %	Coag %	Defensins %
Controls	0	0	5	25
CIRS	25	15	54	7
PCS (-)	0	0	14	28
PCS (+)	42	42	36	36
p-value	0.008	0.03	<0.4	<0.5

BIOMARKERS ESPECIALLY DEFECTIVE ANTIGEN PRESENTATION

Table 3	CD3D Suppressed %	CIRS Biomarkers %	PTSD %	Tubulins %
Controls	<5	<5	<5	<5
CIRS	92	80	30	66
PCS (-)	14	14	0	14
PCS (+)	86	56	28	50
p-value	<0.001	0.046	0.04	<0.05

Induced Immunodeficiency: Inefficient T Cell Receptor Synapse



- Induced suppression of TCR
- Worsens hand off between APC and Adaptive immune response
- Ready for vaccine?

BIOMARKERS: THE MAIN EVENT

Table 4	TGFBR %	Actino %	Endos %	Mycotoxins %
Controls	5	<5	<5	0
CIRS	52	42	28	7
PCS (-)	14	14	0	0
PCS (+)	56	56	64	21
p-value	0.46	0.001	<0.0001	<0.05

Mycotoxins response to exposure

Stage	N=	Per cent
Stage 1	3	7.1
Stage 2	2	7.6
Stage 3	2	*
Stage 4	1	*

Actinomycetes (bacteria!)

Stage	N=	Per cent
Stage 1	18	42
Stage 2	22	15
Stage 3	2	10
Stage 4	3	12

Endotoxins response to exposure

Stage	N=	Per cent
Stage 1	13	27
Stage 2	6	36
Stage 3	5	**
Stage 4	1	*

Shoemaker R, et al. *Medical Research Archives* vol 9 issue 3. Medical Research Archives

RESEARCH ARTICLE

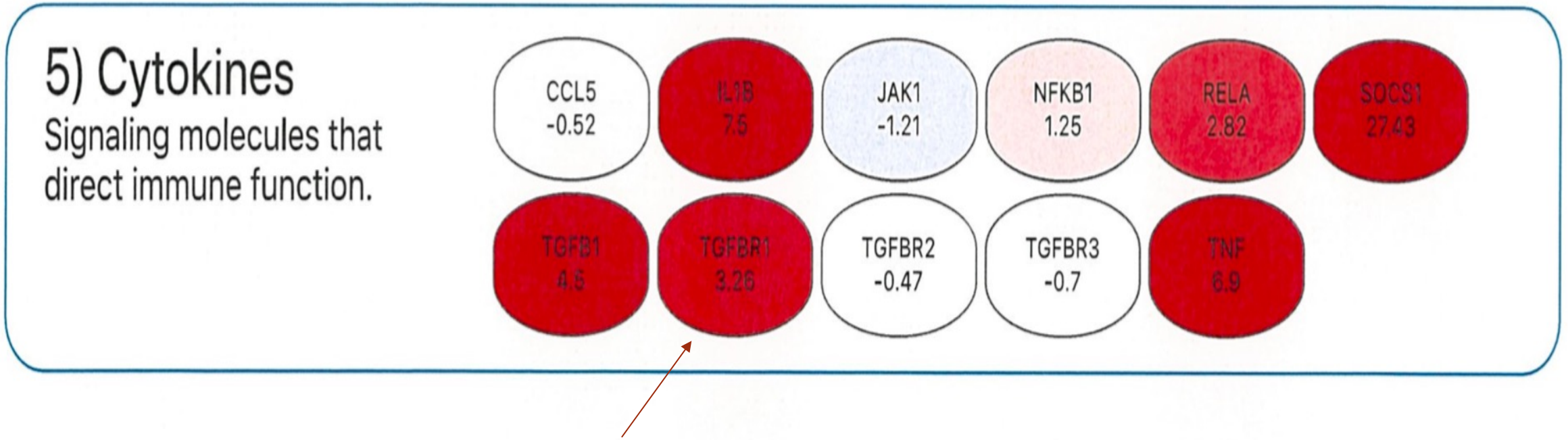
Newer Molecular Methods Bring New Insights into Human- And Building-Health Risk Assessments from Water-Damaged Buildings: Defining Exposure and Reactivity, the Two Sides of Causation of CIRS-WDB Illness

Authors

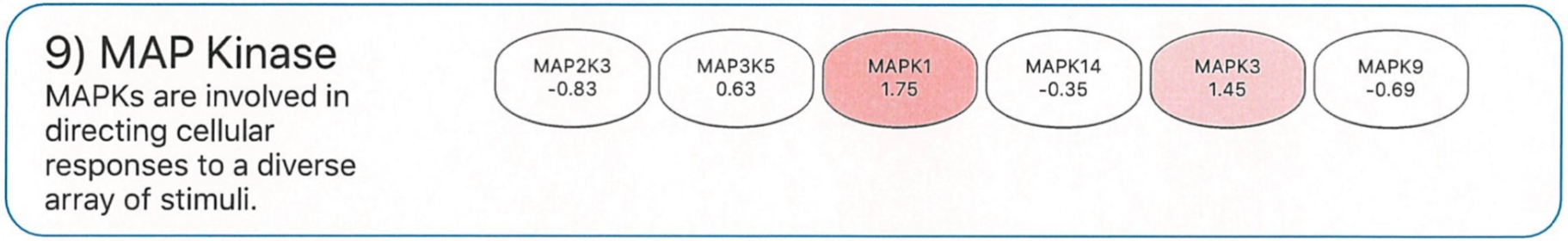
Shoemaker R[1], Neil V[2], Heyman A[3], van der Westhuizen M[4], McMahon S[5], Lark D[6].

BUT PRECISE, SPECIFIC CAUSATION

- TGFBR + MAPK+ VERSUS TGFBR- MAPK +; p < 0.OO21
- TGFBR+ MAPK+ VERSUS TGFBR- MAPK-; p < 0.0002
- COMPARE THOSE NUMBERS TO NEW METHODS PAPER: IF + ACTINOS >15 SPECIES AND MAPK + AND WHEN TGFBR + = 19/19

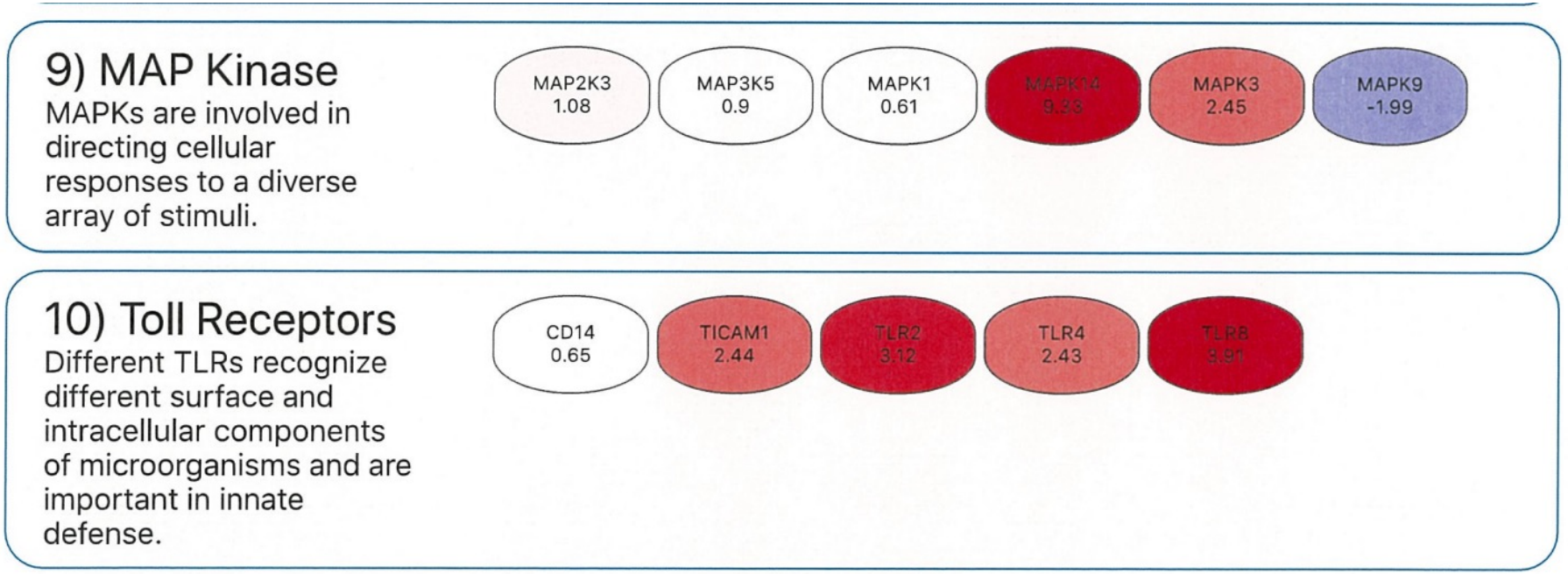


MapKinases – Water Damaged Buildings



- Mycotoxins (molds)
- Actinomycetes (bacteria)
- Endotoxins (inflammagens)

MapKinases – Water Damaged Buildings



- Actinomycetes (bacteria)
- Endotoxins (inflammagens) – CD14 and TLR4

IMMUNOREACTIVITY FOR ACTINOS CREATES METABOLIC INJURY IN CIRS AND PCS

- HOW MANY OTHER ELEMENTS THAT MAKE PEOPLE IN WDB WILL WE DISCOVER HAVE SPECIFIC CAUSATION?
- ENDOS!
- WHAT ABOUT BETA GLUCANS?
- WHY ARE MYCOTOXINS AT THE BOTTOM OF THE LIST?

PRECISE SPECIFIC CAUSATION IN UNTREATED CIRS COMPARED TO PCS

- SEE NEW METHODS AND METAB COMPLICATIONS PAPERS
- MEAN MAPK FOR + ACTINO species >15 = 1.6
- MEAN MAPK FOR + HERTSMI-2 > 10 = 3.7
- IN MEAN + ENDOS > 100, CD14+/TLR 4+ = 86%
- + ACTINO SAMPLE AND MAPK +, AND TGFBR + = 100%
- IN PCS (+), + ACTINOS BY MAPK, TGFBR = 87.5%
- IN PCS (-), + ACTINOS BY MAPK, TGFBR1 = 0

WHAT SIGNIFICANCE IS THERE TO + ACTINOS AND ENDOS IN PCS (+)

- SMALL STUDY, MIGHT BE DUE TO CHANCE
- NO CONTROL GROUP IN STUDY, EXCEPT PCS (-)
- COULD BE THE PCS + GROUP WERE CIRS BEFORE THEY GOT COVID-19
- COULD BE THAT COVID CREATES A RISK FOR CIRS
- COULD BE THAT COVID IS A POST-VIRAL CIRS
  - IF SO, VIP SHOULD WORK (NB: IT DOES)
  - LOOK FOR TGFBR SGNALING

FROM THE COVID LITERATURE SEE JAIN 2021 IN BIBLIOS

- COVID HAS GLOBALLY DYSREGULATED IMMUNE PATHWAYS
- CYTOKINES, COMPLEMENT AND COAG; SEE RYAN, 2016
- GLOBAL REDUCTION OF PRODUCTION OF PROTEIN AND ENERGY; SEE RYAN 2016
- TGF BETA PATHWAY SIGNIFICANTLY UPREGULATED
- CONFIRMATION BY REPRODUCTION OF FINDINGS VALIDATES RYAN

FROM THE COVID LITERATURE-2 SEE XIONG 2020 IN BIBLIOS

- TGF BETA INDUCED BY COVID
- TGF B SUPPRESSES IFN, TRIGGERING SEVERE PATHOLOGY
- INFLAMMATORY RESPONSES IN BLOOD ARE DIFFERENT FROM LAVAGE FLUID
- GENOMICS SHOWS ENRICHMENT OF PARTICULAR PATHWAYS
- SUPPRESS OF AXON GUIDANCE AND mRNA PROCESSES
- TGF BETA SIGNALING BLOCKS APOPTOSIS, ENHANCES MYOFIBROBLAST DIFFERENTIATION

FROM THE COVID LITERATURE-3 SEE CATANZARO 2020 IN BIBLIOS

- CYTOKINE STORM IS DYSREGULATED INNATE IMMUNE RESPONSE
- NAÏVE T CELLS PREDOMINATE OVER T REGS
- VIRAL RNAs ARE RECOGNIZED AS PAMPS BY TLR WHICH ACTIVATE SIGNALING IN CD14+ MONOCYTES (WORSE IF CD 14 IS ALREADY UPREGULATED?)

STUDY SUMMARY

- WE SEE THAT PCS (+) APPROACHES UNTREATED CIRS
- WE SEE THAT PCS (-) APPROACHES KNOWN CONTROLS
- WE SEE THE SAME PATTERN OF MHM IN PCS (+) AND CIRS
- WE SEE THE ROLE OF TGF B SIGNALING CONSERVED
- WE SEE INFLAM CHANGE OF HOST WITH MHM = PRIMING
- CONSISTENT WITH POST-VIRAL CIRS
- THE RESULTS WARRANT A LARGER TRIAL!

FOCUS ON SYMPTOMS

- PCS, CIRS MULTISYSTEM, MULTI-SYMPTOM
- LEAST RELIABLE CLINICAL PARAMETER
- SO MANY TO REMEMBER, DAY TO DAY CHANGE
- DAILY RE-EXPOSURES UNKNOWN EFFECTS
- PROBLEMS ARISE EVERYWHERE BLOOD FLOWS
- UNUSUAL IS USUAL: TRPV2, SHOCKS, EXTREMITY SPASMS, LIGHTNING BOLT PAIN

FOCUS ON VCS

- PCS (-) DON'T HAVE DEFICITS
- PCS (+) 75% DO
- WHAT IS EXPOSURE IN PCS (+)
  - 56% ACTINO
  - 64% ENDOS
  - 20% MYCOS
- WE DON'T KNOW IF VCS (+) PCS(+) CORRECT WITH RX
- DID VCS DEFICIT START BEFORE OR AFTER COVID

Visual Contrast Test

VCS Left Eye

	A	B	C	D	E
9	⊗	⊗	⊗	⊗	⊗
8	⊗	✓	✓	⊗	⊗
7	⊗	✓	⊗	⊗	✓
6	✓	✓	✓	✓	⊗
5	✓	✓	✓	✓	✓
4	✓	✓	✓	✓	✓
3	✓	✓	✓	✓	✓
2	✓	✓	✓	✓	✓
1	✓	✓	✓	✓	✓

VCS Right Eye

	A	B	C	D	E
9	⊗	⊗	⊗	⊗	⊗
8	✓	⊗	✓	⊗	⊗
7	✓	⊗	⊗	✓	⊗
6	✓	✓	✓	⊗	⊗
5	✓	✓	✓	✓	⊗
4	✓	✓	✓	✓	✓
3	✓	✓	✓	✓	✓
2	✓	✓	✓	✓	✓
1	✓	✓	✓	✓	✓

Result: Fail

FOCUS ON MHM AND PROLIFERATIVE PHYSIOLOGY

- MHM 0% IN PCS (-) AND 100% IN PCS (+)!
- CRUCIAL POINT: IF IRS2 > 0, THEN PROLIF
  - MEASURE ANION GAP AT TIME 0; GLUCOLA 1, 2 HOURS
  - IF ANION GAP RISES, LIKELY PROLIFERATIVE
  - METABOLIC ACIDOSIS, PASP UP, T REGS DOWN, NA UP
- IF IRS2 <0, THEN DIVERSION TO BSP
  - INCREASING INSULIN RESISTANCE OBESITY, DM
- MHM CORRECTS WITH CIRS , REVERSES WITH VIP

SPECIAL SPIN WHEN ILLNESS IS POST-VIRAL

- WARFARE OVER APOPTOSIS: PACKAGE THE TRASH
- VIRUS SAYS NO APOPTOSIS; INFECTED CELL SAYS YES
- BCL2 BLOCKS VIRAL-INDUCED APOPTOSIS
- AUTOPHAGY MAY BE PLAYING A ROLE
- NECROPTOSIS: NO PACKAGING THE TRASH

TREATMENT PROTOCOL-1

- GENIE IS YOUR GUIDE
- VERIFY MHM AND PROLIF PHYSIO
- IF ACTINOS, ENDOS OR MYCOS, DO SAMPLING
- IF IMMUNOREACTIVITY, WELCHOL TWO WEEKS AND CONTINUE
- SANITIZE HOME AND WORKPLACE
- IF MISMATCH IKAROS TO VIPR1, USE LOW DOSE VIP
- TWO WEEKS OF OMEGA-3 IF VEGF LOW OR MMP9 HIGH

TREATMENT PROTOCOL-2

- MARCoNS NOT A PLAYER FOR SHORT DURATION ILLNESS
- EDTA 0.25% if illness > 4 months and culture positive
- NO ANTIFUNGALS
- RAMP UP TO 12 SPRAYS A DAY VIP

For More Information

- www.survivingmold.com
- www.progenedx.com
- Art and Science of CIRS Medicine; Ebook available 9/25/20
- Authors: Ritchie Shoemaker MD,
  Scott McMahon MD
  Andrew Heyman MD, MHSA

Thanks to:

- Jimmy Ryan PhD
- Debbie Waidner, data collation
- Paul Taylor, Surviving Mold