Research Essentials Talk

UF Jacksonville

August 4, 2020

The Southwestern Surgical Congress

Presidential Address: Imagination trumps knowledge

Frederick A. Moore, M.D.*

The American Journal of Surgery (2010) 200, 671–677

Strategy for Translational Team Science

Testable Cartoons

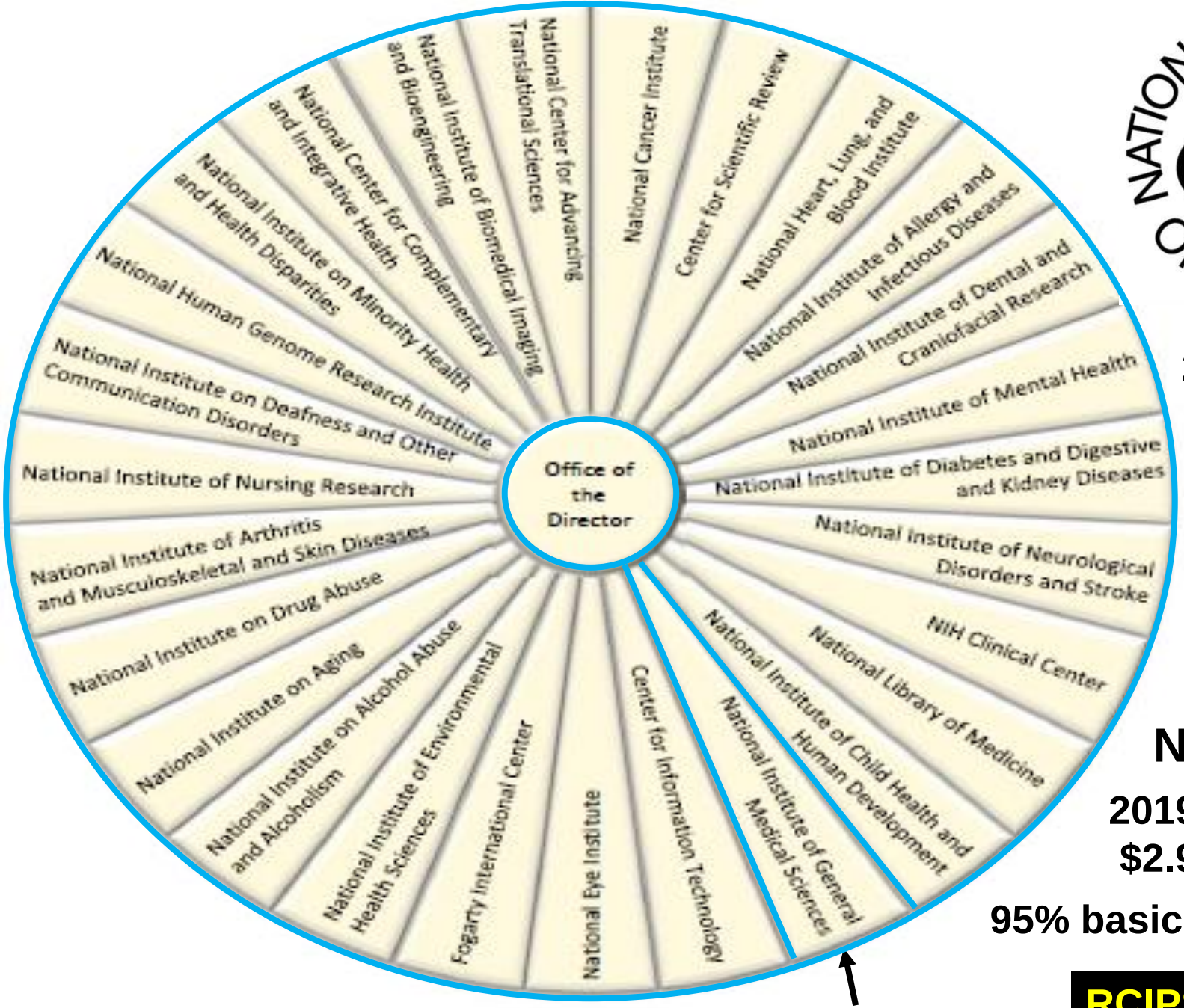
Imagination

The role of NIGMS P50 sponsored team science in our understanding of multiple organ failure

Frederick A. Moore, MD, Ernest E. Moore, MD, Timothy R. Billiar, MD, Yoram Vodovotz, PhD, Anirban Banerjee, PhD, and Lyle L. Moldawer, PhD, ***Gainesville, Florida***

J Trauma Acute Care Surg 2017

Only discuss results related to the next cartoon



NATIONAL INSTITUTES OF HEALTH

21 Institutes

6 Centers

NIGMS

2019 budget
$2.9 billion

95% basic, 5% clinical

RCIPS Grants

National Institute of General Medical Sciences (NIGMS)

Research Centers in Injury and Peri-operative Sciences
"P50 RCIPS Grants"

Team Science Around a Common Theme

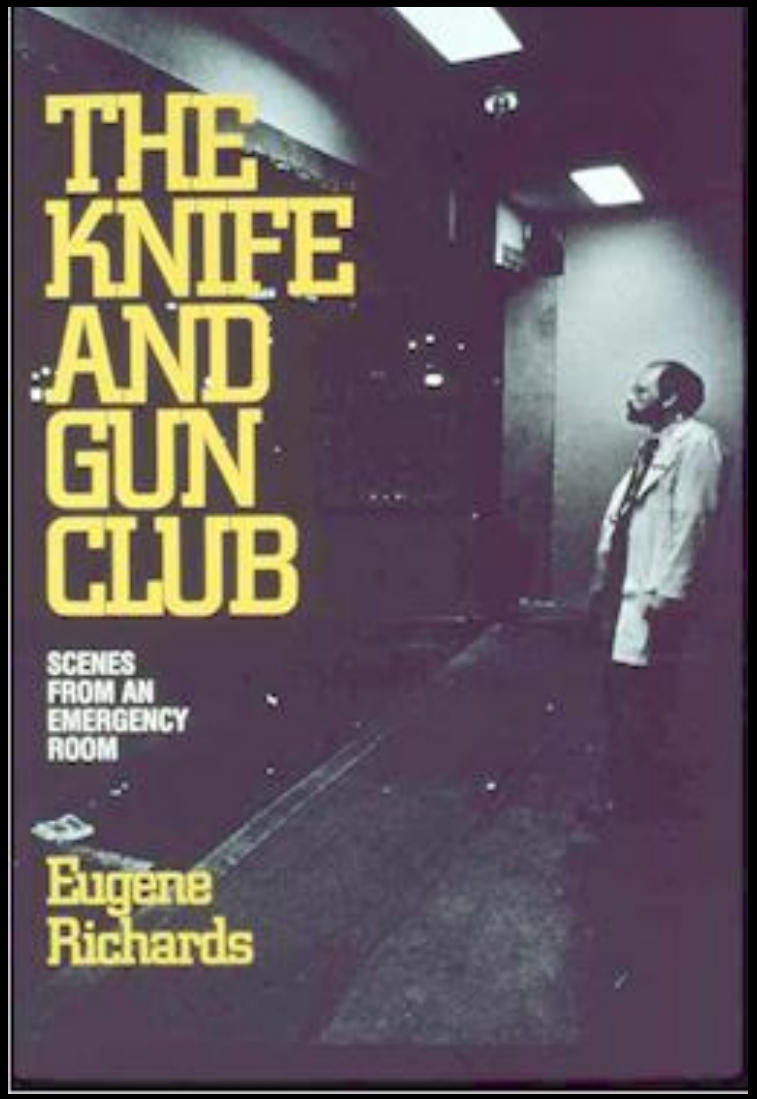
3-5 Projects Led by Established Scientists

Value-added Beyond Collection of RO1 Projects

Primary Purpose ⟶ **Transform Knowledge**

University of Colorado
1979-1996

Denver General (DG)



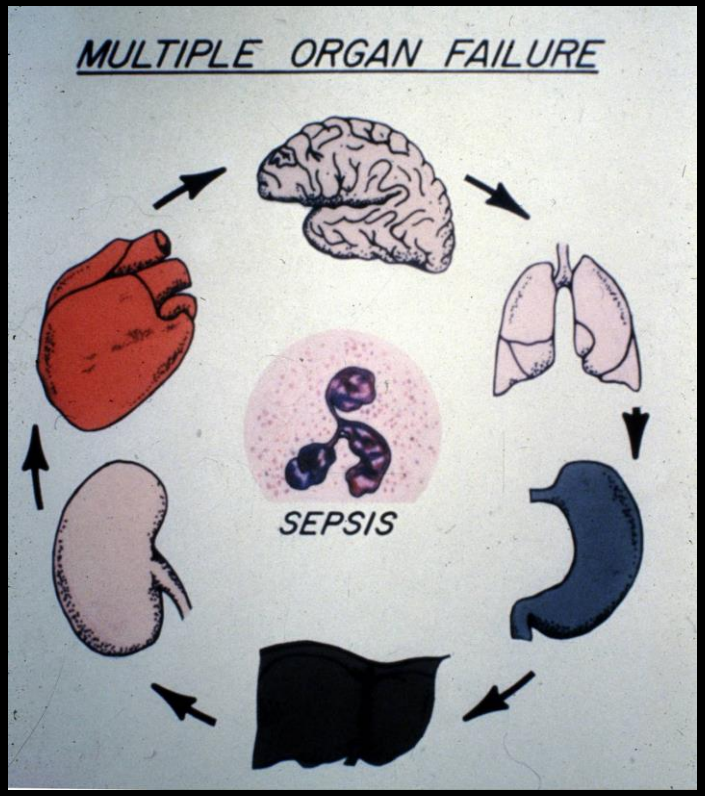
Research was a core value

MULTIPLE ORGAN FAILURE

B. Eiseman, M.D., F.A.C.S., R. Beart, M.D., *and* L. Norton, M.D., F.A.C.S.,
Denver, Colorado

Surg Gyn Obstet 1977

Confusing & Important Topic

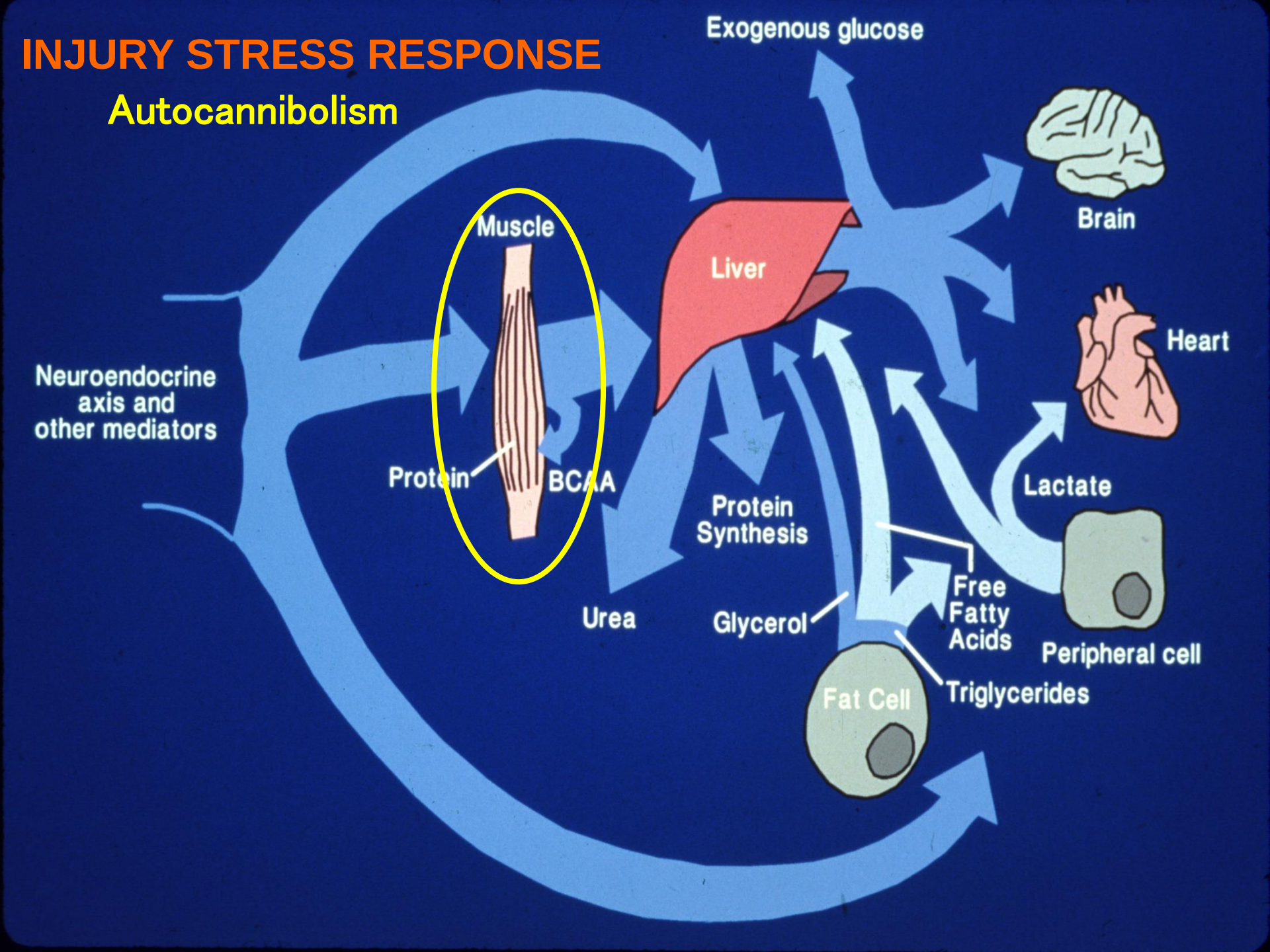


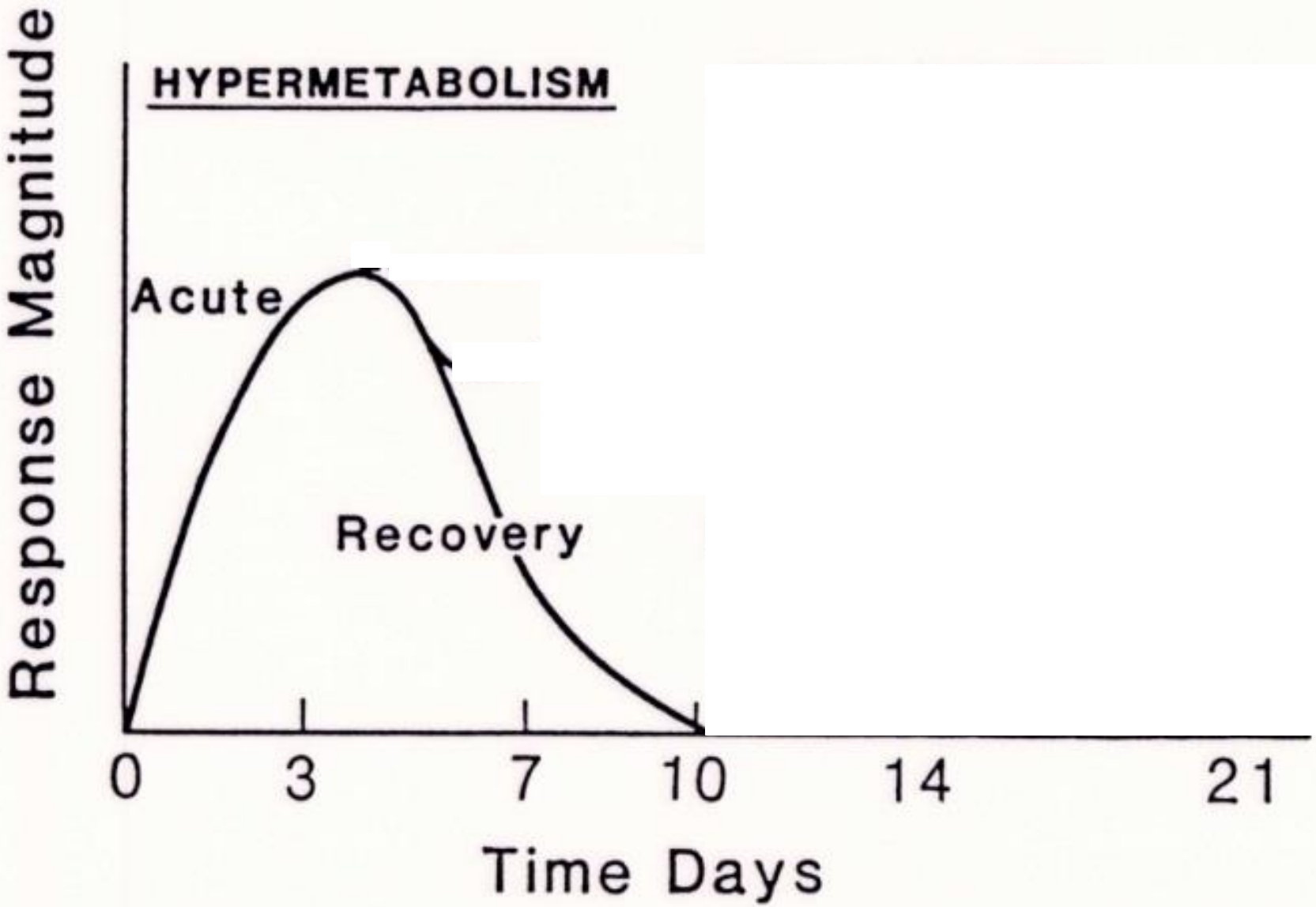
Became Our Research Focus

Ben Eiseman

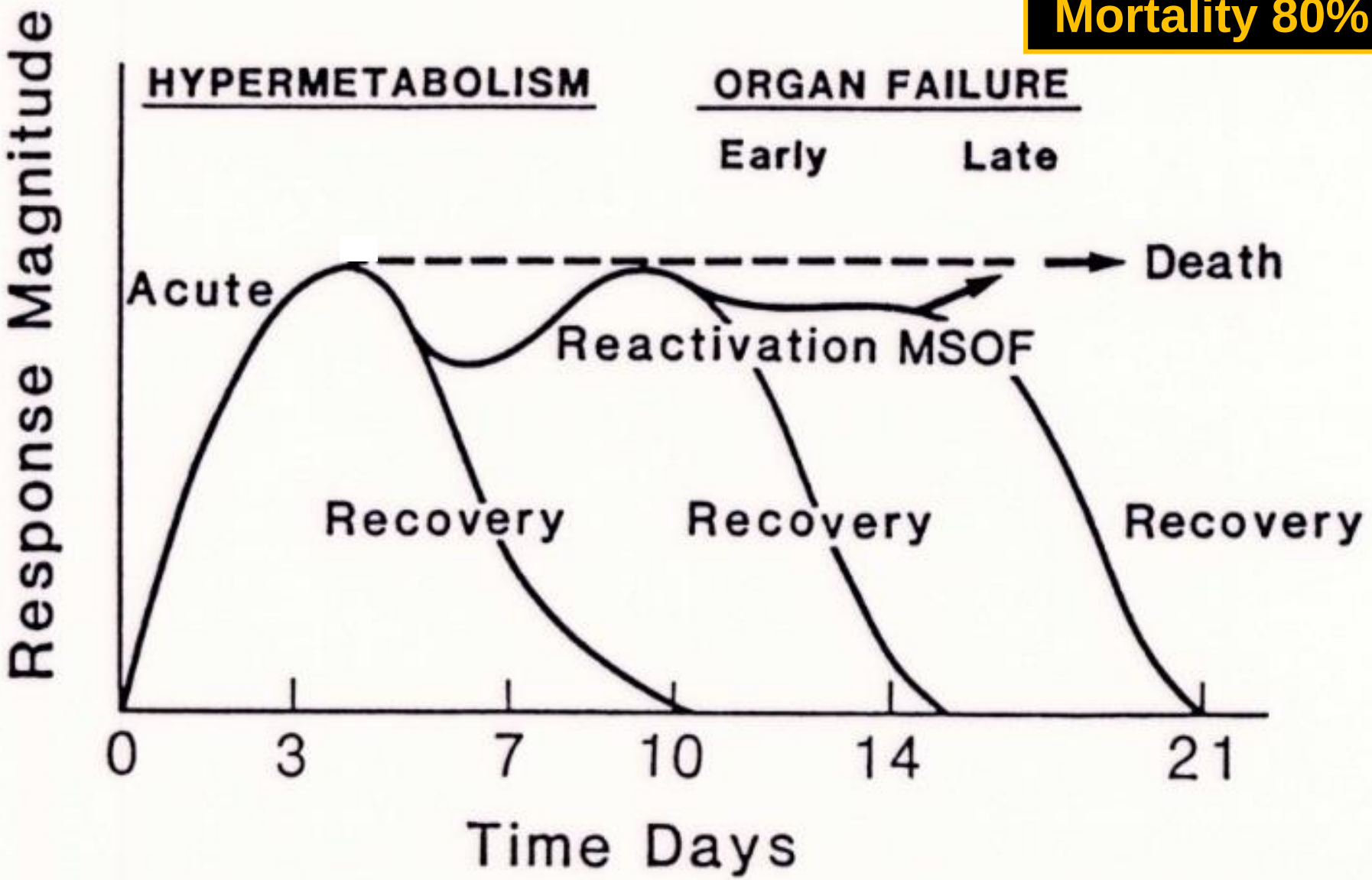
INJURY STRESS RESPONSE

Autocannibolism




HYPERMETABOLISM
Response Magnitude
Acute
Recovery
0
3
7
10
14
21
Time Days

MOF
Mortality 80%



JL Meakins

Host Response to Blunt Trauma: Interrelationships of Anergy, Depressed Neutrophil Function, Nutritional Status and Sepsis

NV Christou, MD, PhD; APH McLean MD and JL Meakins

J Trauma 1980

Linked to Immunosuppression & Later Sepsis

RF Edlich

The influence of catabolism on immunocompetence in burned patients

J.M. Hiebert MD, M. McGough, BA, G. Rodeheaver, PhD, J. Tobiasen,MA
M.T. Edgerton, MD and R.F. Edlich MD, PhD

Surgery 1979

Reversed by Nutritional Support (TPN)

Stan Dudrick

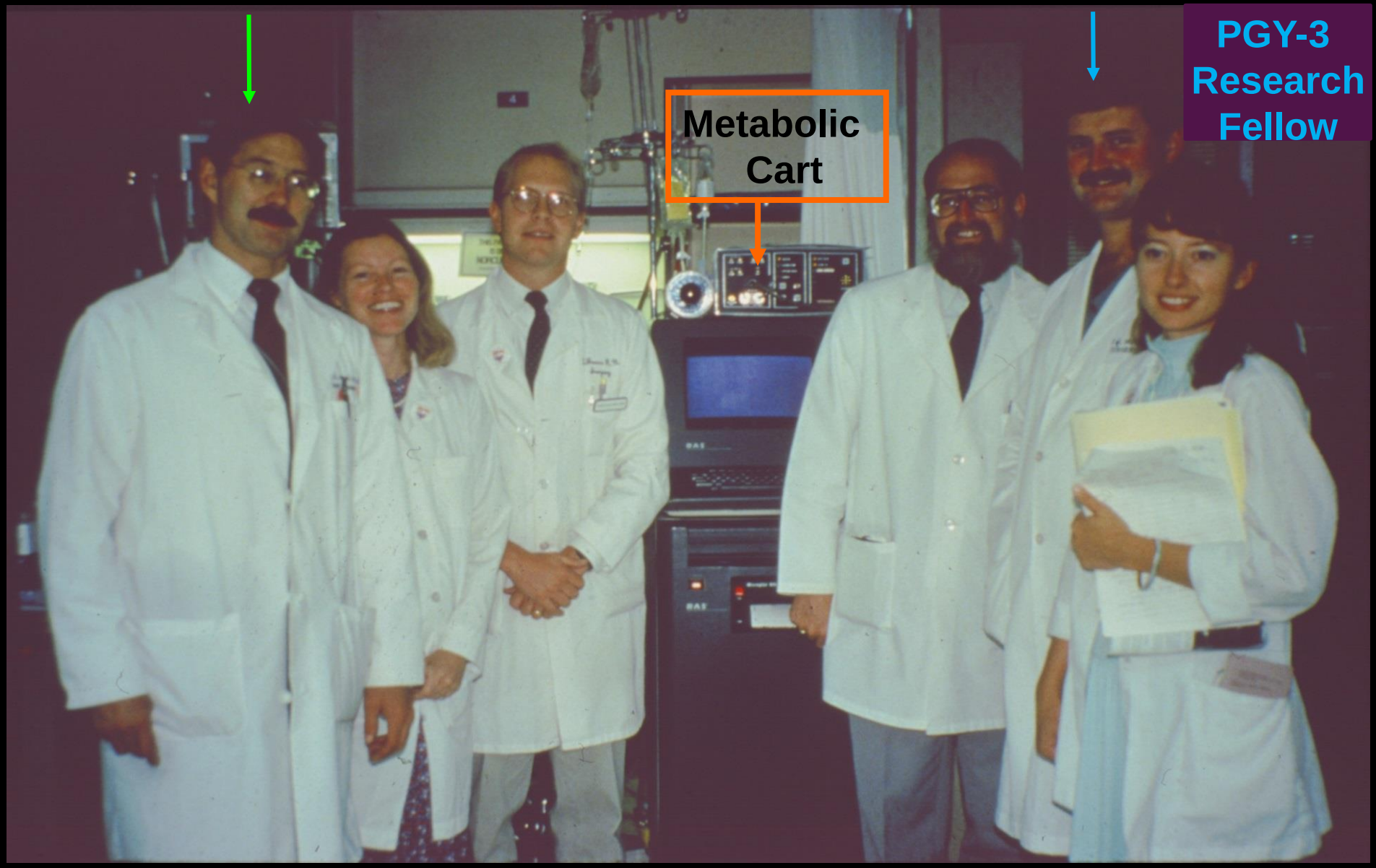
Effects of Protein Depletion and Repletion on Cell-mediated Immunity in Experimental Animals

John M. Daly, MD, Stanley J. Dudrick, MD, Edward M. Copeland, MD.

Ann Surg 1978

"Golden Age" of TPN

Nutrition Support Team
Denver General Hospital



Cartoon # 1

Injury Stress Response

Acute Protein Malnutrition

↓ Muscle Mass

↓ Visceral Protein

↓ Organ Function

↓ Immune Response

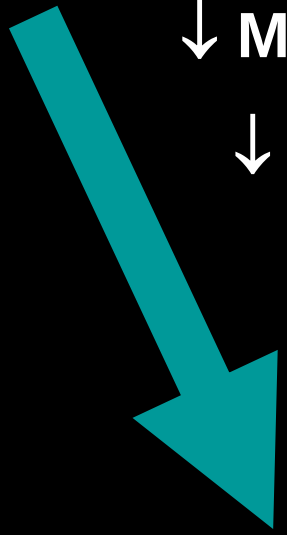
Infection

Multiple Organ Failure

Hypothesis

Acute Protein Malnutrition

Nutritional Support



↓ Muscle Mass

↓ Visceral Protein

↓ Organ Function

↓ Immune Response

Infection

Multiple Organ Failure

Benefits of Immediate Jejunostomy Feeding after Major Abdominal Trauma—A Prospective, Randomized Study

ERNEST E. MOORE, M.D., AND TODD N. JONES, B.S.N.

J Trauma 1986

Early TEN vs. Delayed TPN

Decreased Infections

TEN versus TPN following Major Abdominal Trauma—Reduced Septic Morbidity

FREDERICK A. MOORE, M.D., ERNEST E. MOORE, M.D., TODD N. JONES, R.N., BRIAN L. McCROSKEY, M.D., AND VERLYN M. PETERSON, M.D.

J Trauma 1989

Early TEN vs. Early TPN

Decreased Infections

Is TEN good or is TPN bad ?

Multiple Organ Failure in Polytrauma Patients

E. FAIST, M.D., A.E. BAUE, M.D., H. DITTMER, M.D., AND G. HEBERER, M.D.

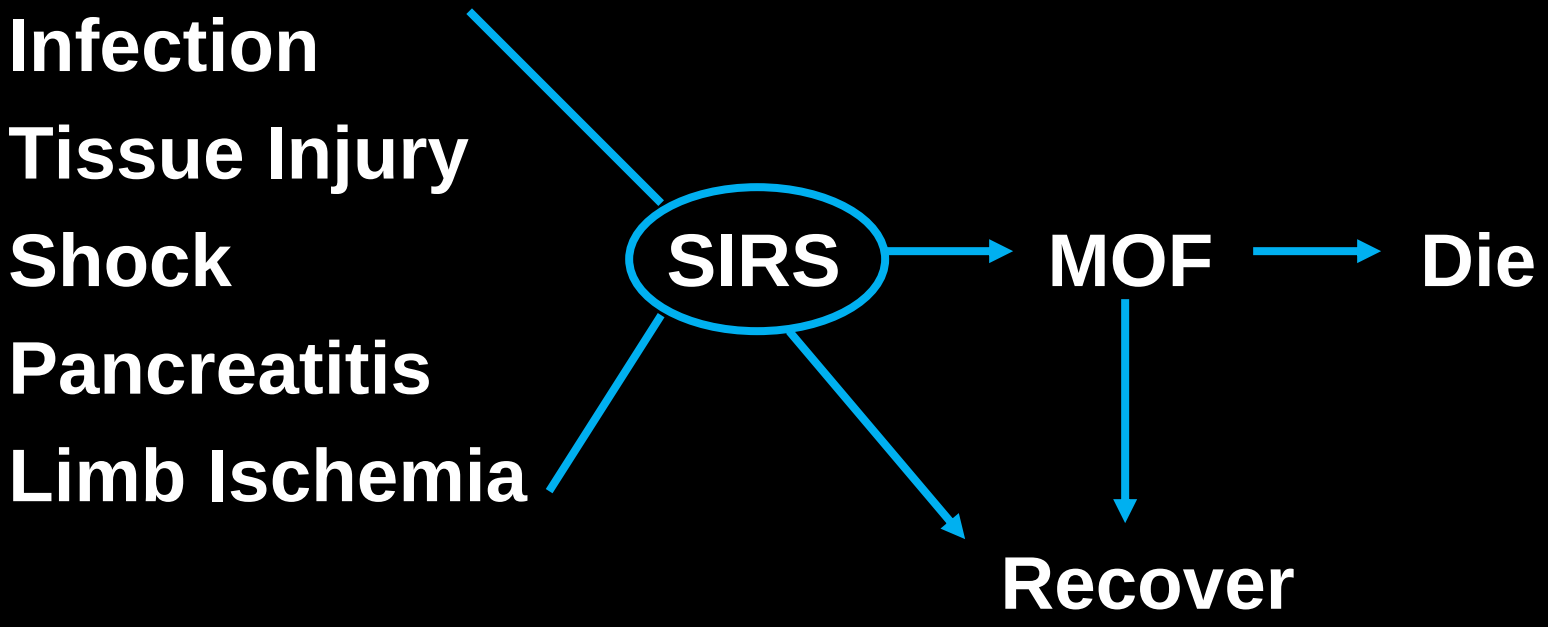
J Trauma 1983

Eugene Faist

MOF can occur without infection

Visiting Professor

SYSTEMIC INFLAMMATORY RESPONSE



“SEPSIS SYNDROME”

Hemorrhagic Shock Induces Bacterial Translocation from the Gut

JOHN WILDER BAKER, M.D., EDWIN A. DEITCH, M.D., F.A.C.S., MA LI, M.D., RODNEY D. BERG, PH.D., AND ROBERT D. SPECIAN, PH.D.

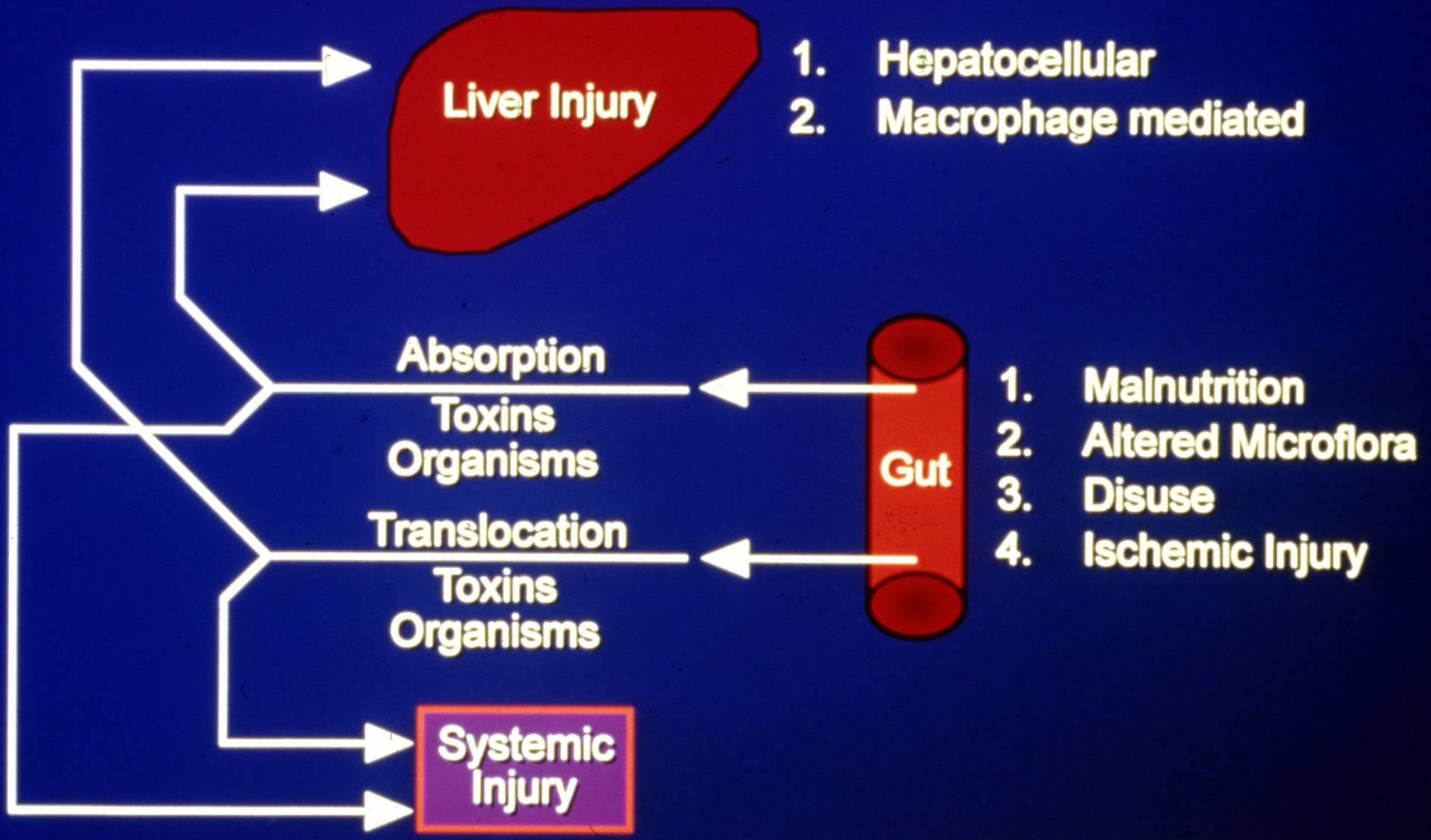
J Trauma 1988

Edwin A. Deitch

Bacterial Translocation causes SIRS

Visiting Professor

Gut Hypothesis

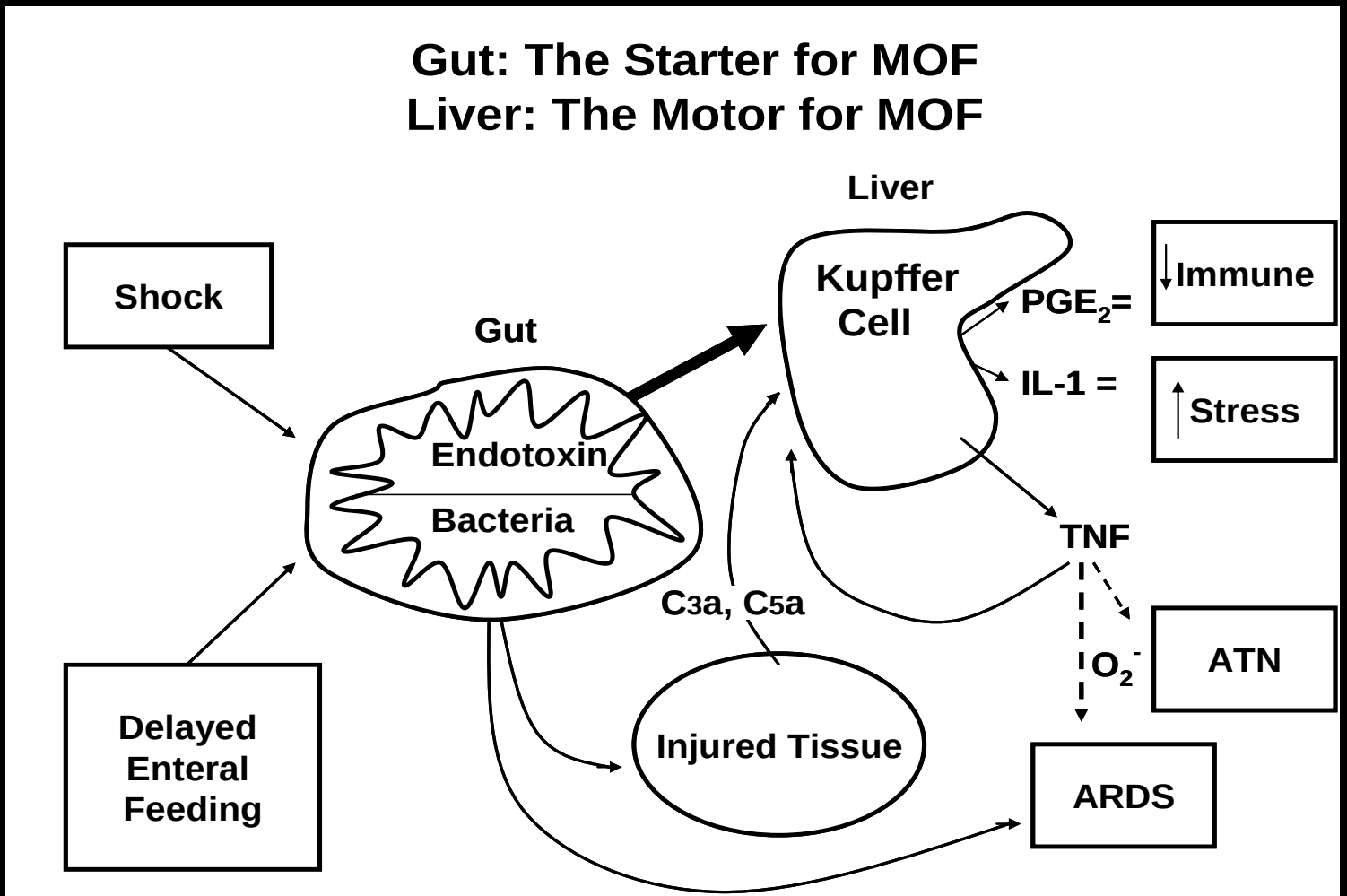


TEN versus TPN following Major Abdominal Trauma—Reduced Septic Morbidity

FREDERICK A. MOORE, M.D., ERNEST E. MOORE, M.D., TODD N. JONES, R.N., BRIAN L. McCROSKEY, M.D., AND VERLYN M. PETERSON, M.D.

J Trauma 1989

Cartoon # 2



TEN versus TPN following Major Abdominal Trauma—Reduced Septic Morbidity

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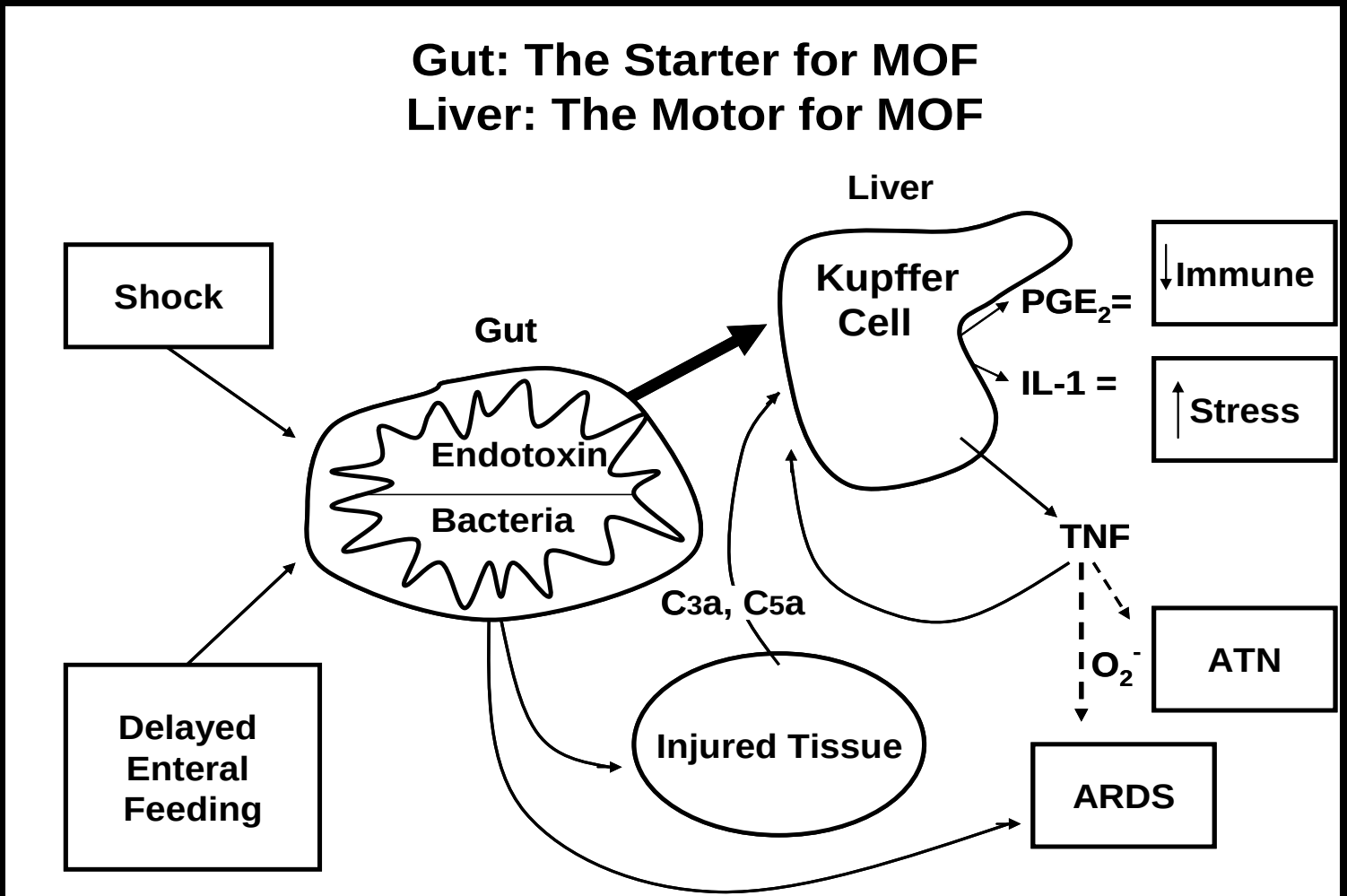
J Trauma 1989

Testable hypothesis:



TEN versus TPN following Major Abdominal Trauma—Reduced Septic Morbidity

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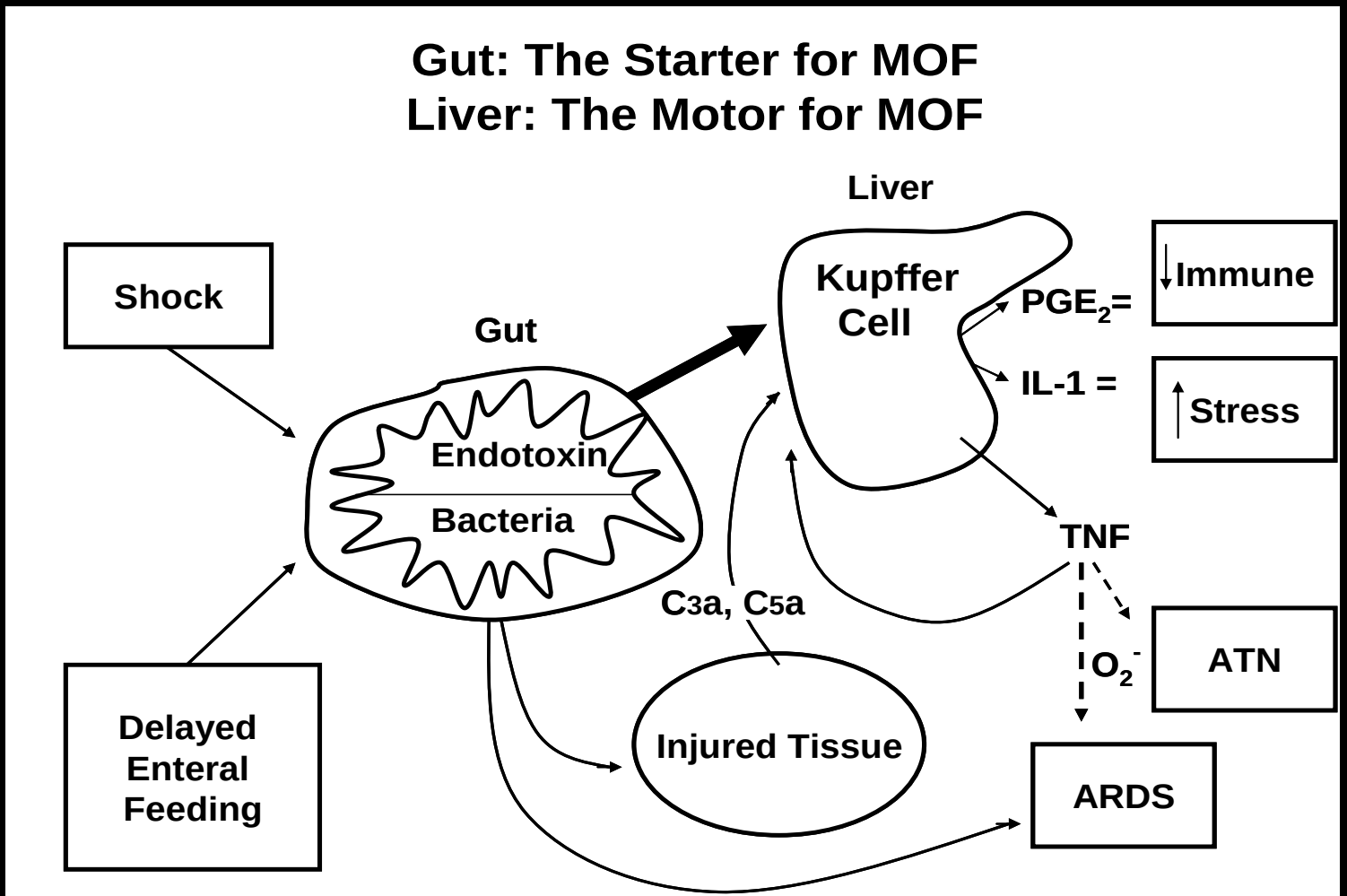
J Trauma 1989

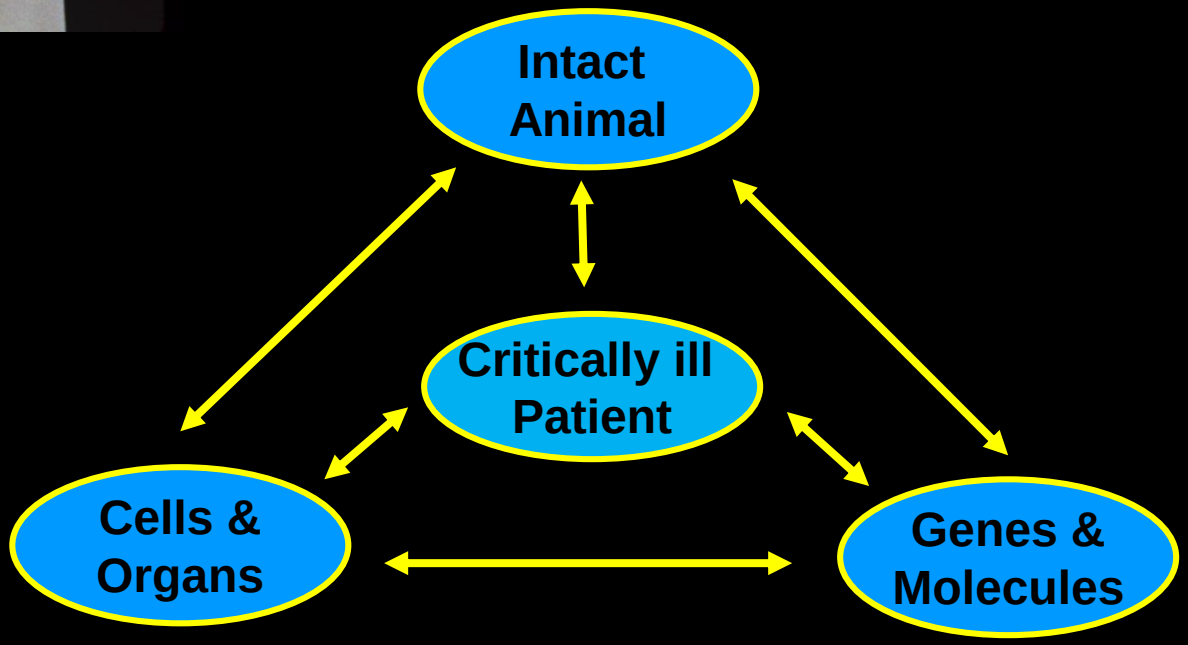
Testable hypothesis: bacterial translocation via portal vein



Alden Harken

TRAUMA RESEARCH CENTER
UNIVERSITY OF COLORADO

New Chairman



NIGMS P50 Team Science Grant

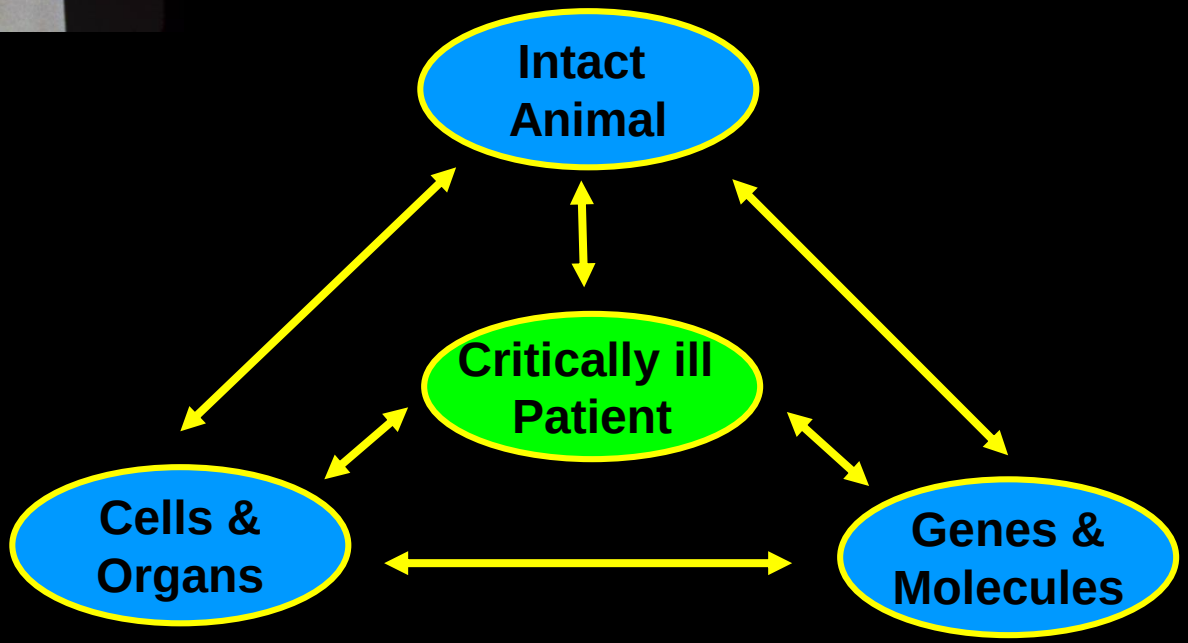
Alden Harken

Study Your Patients!

TRAUMA RESEARCH CENTER

DG SICU - CLINICAL CORE

"Focus"



Organize ICU to be Research Lab

Clinical Specialist Position

Jim Heanel

RIGHT-HAND MAN
Consider It Done!

Standard Operating Procedures (SOPs)

- Sedation
- Analgesia
- ICP Management
- Pulmonary Care
- Ventilator Management and Weaning
- ARDS Rescue Protocol
- Shock Resuscitation Protocol
- Enteral Feeding Protocol
- Stress Ulcer Prophylaxis
- DVT Prophylaxis
- Bedside Procedure Team
- Metabolic Cart Studies
- Antibiotic Protocol
- Electrolyte Replacement

Gut Bacterial Translocation via the Portal Vein: A Clinical Perspective with Major Torso Trauma

FREDERICK A. MOORE, M.D., ERNEST E. MOORE, M.D., RENATO POGGETTI, M.D.,
OLIVER J. McANENA, M.D., VERLYN M. PETERSON, M.D., CHARLES M. ABERNATHY, M.D.,

J Trauma 1991

20 Torso Trauma Resuscitation Patients

Clinical Relevance

Hypothesis: bacterial translocation via portal vein is driving mechanism in MOF

Gut Bacterial Translocation via the Portal Vein: A Clinical Perspective with Major Torso Trauma

FREDERICK A. MOORE, M.D., ERNEST E. MOORE, M.D., RENATO POGGETTI, M.D.,
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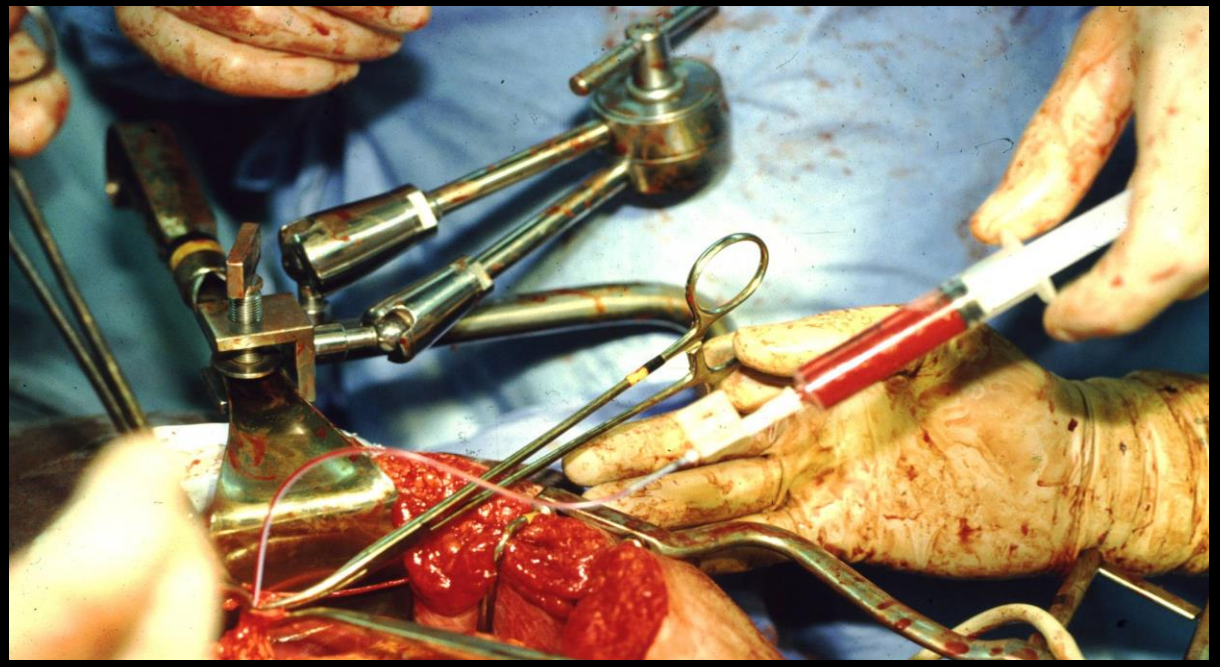
J Trauma 1991

20 Torso Trauma Resuscitation Patients

Portal Vein Catheters & Sampled Blood X 5 days



Hypothesis: bacterial translocation via portal vein is driving mechanism in MOF

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J Trauma 1991

20 Torso Trauma Resuscitation Patients
Portal Vein Catheters & Sampled Blood X 5 days

Win-Win Hypothesis

Found no endotoxin or bacteria in portal vein

Cartoon # 3

Back to the Drawing Board

First Hit

Shock + Tissue Injury

Systemic Inflammatory Response

Vulnerable

Second Hit

MULTIPLE ORGAN FAILURE

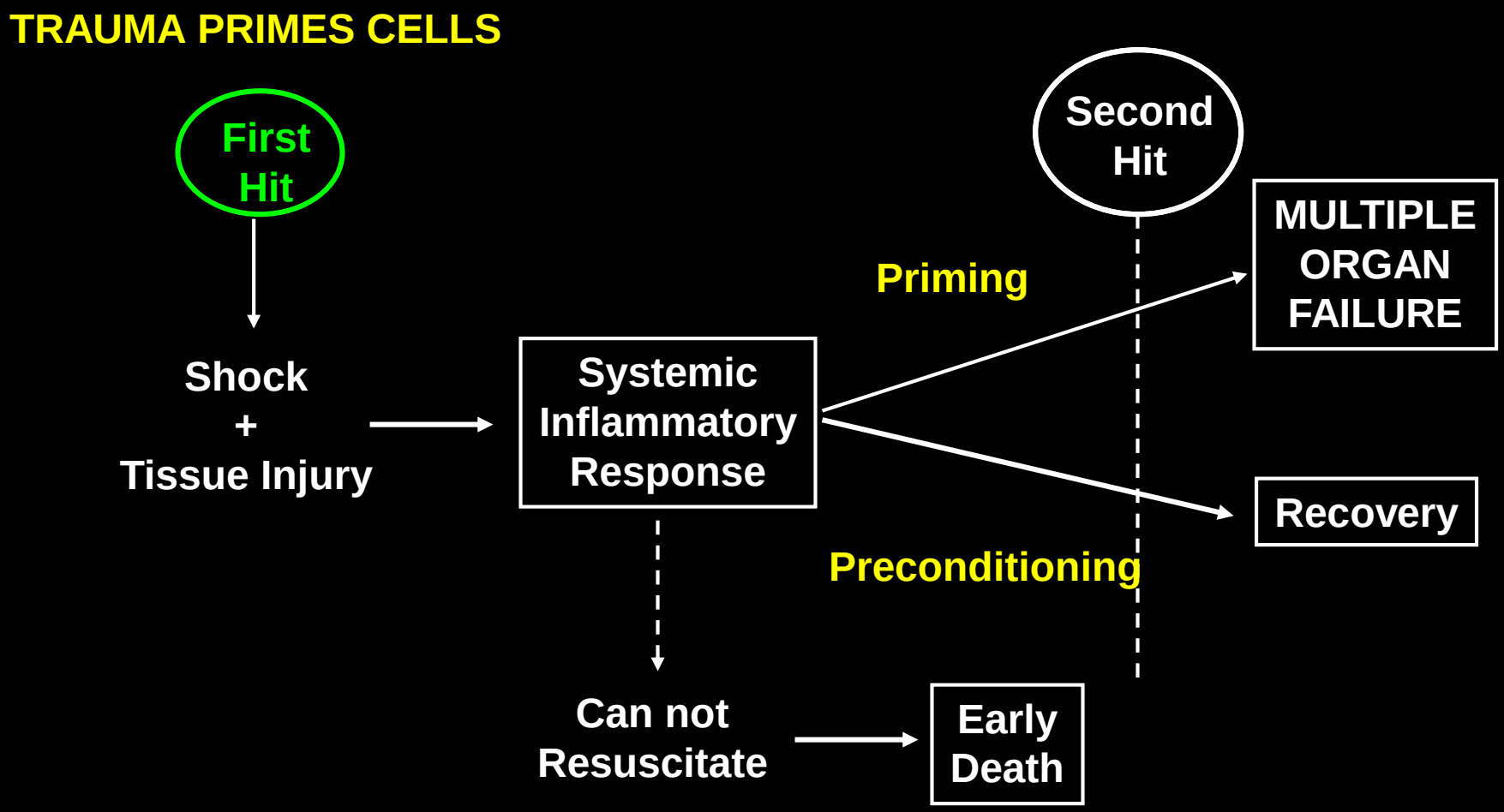
Recovery

Protected

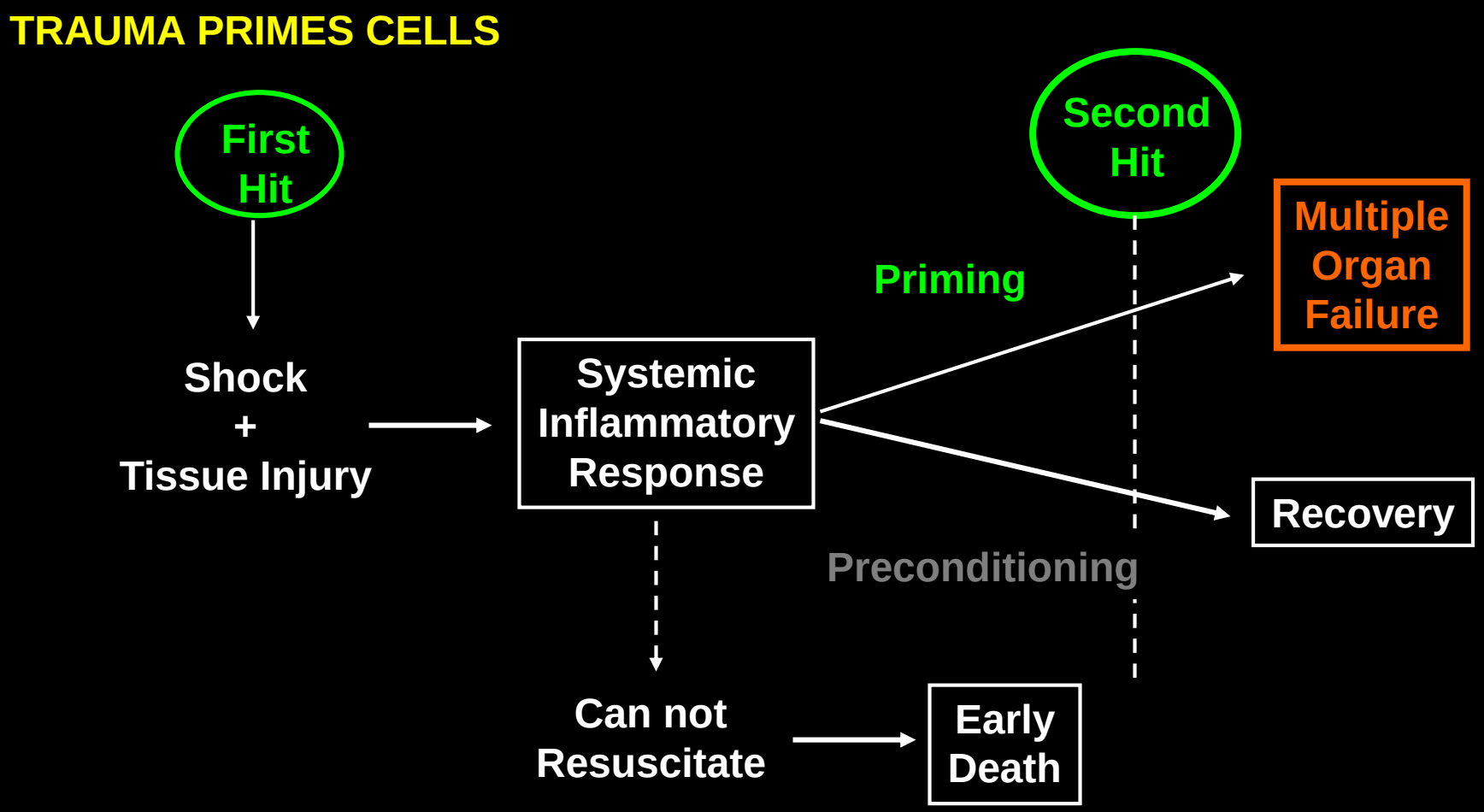
Can not Resuscitate

Early Death

Cartoon for P-50 Trauma Center Grant



The "Two-Hit" Model of Neutrophil Activation



POSTINJURY NEUTROPHIL PRIMING AND ACTIVATION STATES: THERAPEUTIC CHALLENGES

Botha AJ, Moore FA, Moore EE, Fontes B, Banerjee A, and Peterson VM:

***Shock* 1993**

Wrote a Review Article

Abrie Botha

UK General Surgeon

Pete Peterson

Pediatric Hematologist

Lung Injury Is a Reversible Neutrophil-Mediated Event Following Gut Ischemia

Renato S. Poggetti, MD; Frederick A. Moore, MD; Ernest E. Moore, MD; Denis D. Bensard, MD; Benjamin O. Anderson, MD; Anirban Banerjee, PhD

Arch Surg 1992

Renato Poggetti

1st Research Fellow

Created clinically relevant lab model

Gut Ischemia Reperfusion Induced

Reversible Acute Lung Injury

THE POSTISCHEMIC GUT SERVES AS A PRIMING BED FOR CIRCULATING NEUTROPHILS THAT PROVOKE MULTIPLE ORGAN FAILURE

Ernest E. Moore, MD, Frederick A. Moore, MD, Reginald J. Franciose, MD, Fernando J. Kim, MD, Walter L. Biffl, MD, and Anirban Banerjee, PhD

J Trauma 1994

45 Min SMA Occlusion

Activates Gut PLA_2

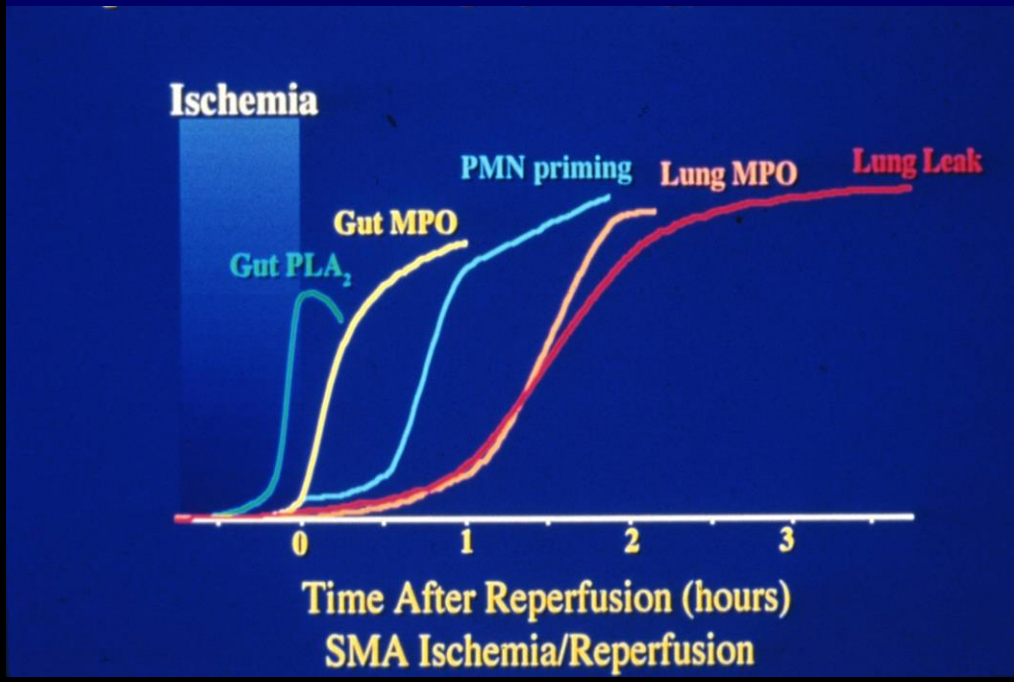
Sequesters PMN's in Gut

Primes Circulating PMN's

Sequesters PMN's in Lung

Reversible Lung Injury

Pathophysiologic Sequence



Max Lung Leak at 12 hours and back to control by 24 hours

THE POSTISCHEMIC GUT SERVES AS A PRIMING BED FOR CIRCULATING NEUTROPHILS THAT PROVOKE MULTIPLE ORGAN FAILURE

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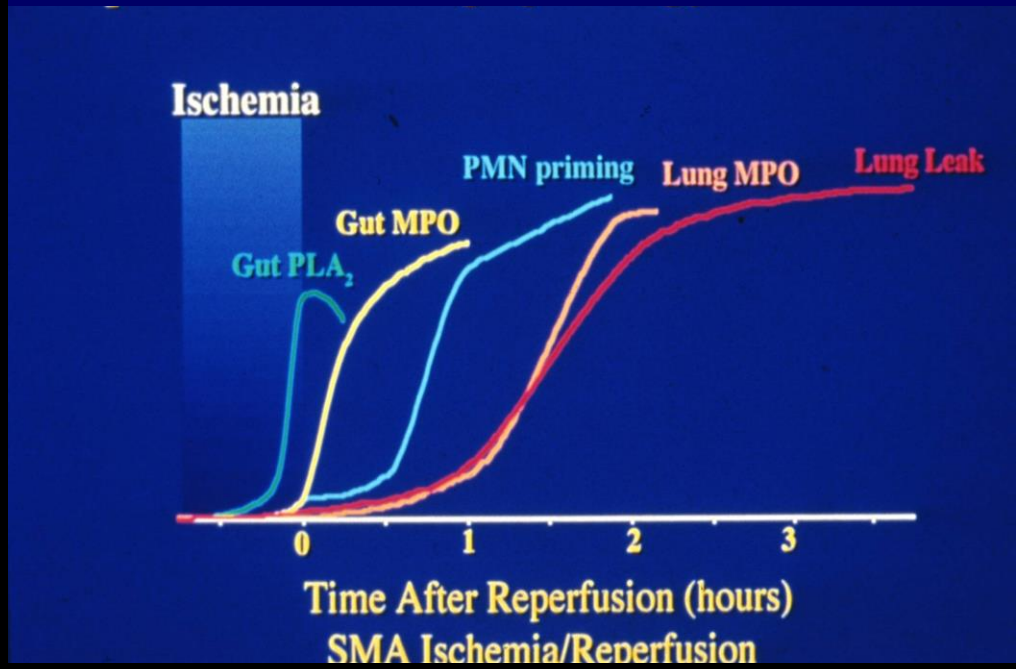


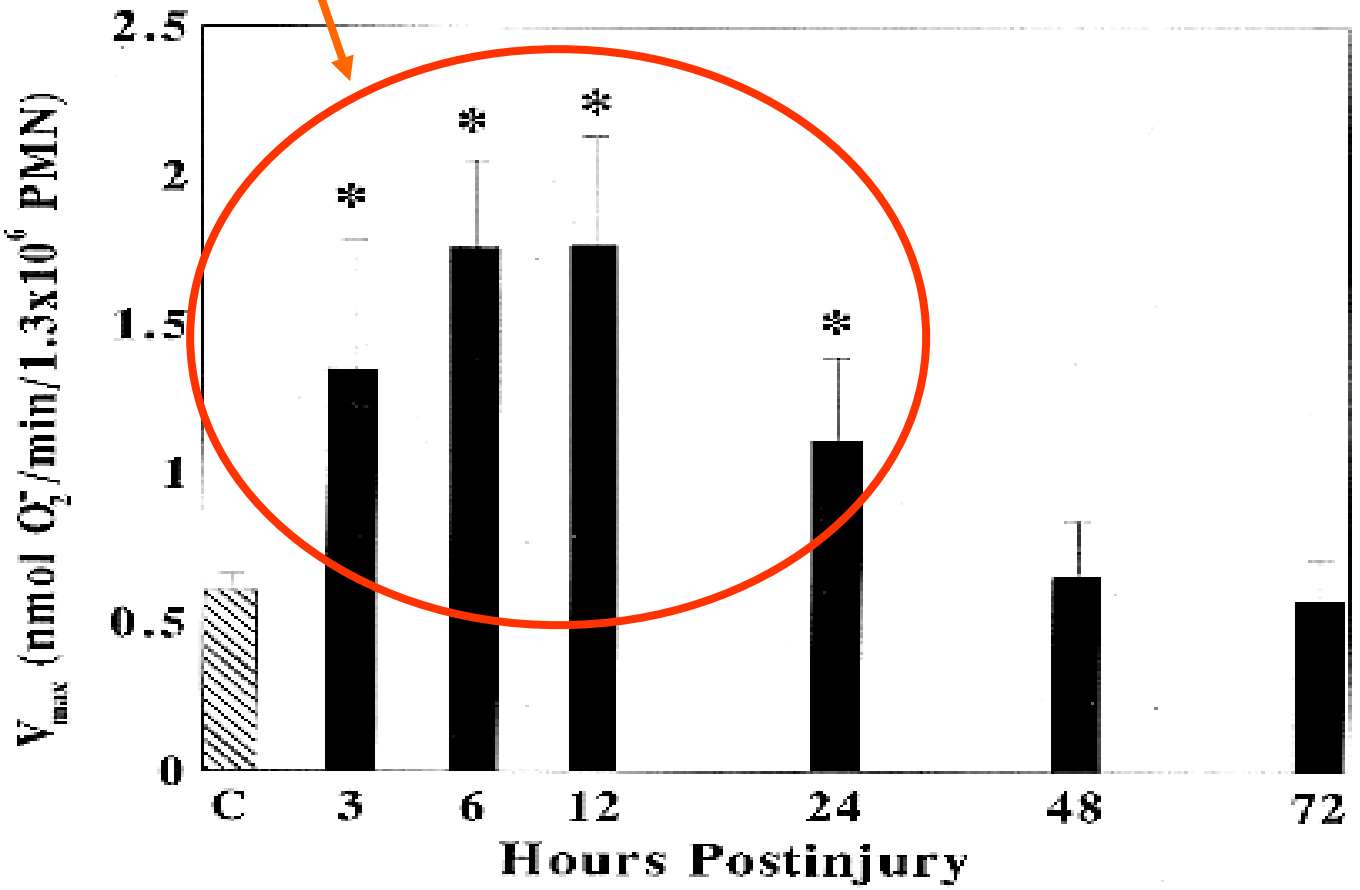
2nd hit of LPS IP at 6 hours → MOF and death

Postinjury neutrophil priming and activation: An early vulnerable window (24 hours)

Abraham J. Botha, MD, Frederick A. Moore, MD, Ernest E. Moore, MD, Fernando J. Kim, MD, Anirban Banerjee, PhD, *and* Verlyn M. Peterson, MD,
Denver, Colo.

Surgery 1995

V max of Superoxide Production after fMLP Stimulation



Postinjury neutrophil priming and activation: An early vulnerable window

Abraham J. Botha, MD, Frederick A. Moore, MD, Ernest E. Moore, MD, Fernando J. Kim, MD, Anirban Banerjee, PhD, *and* Verlyn M. Peterson, MD,
Denver, Colo.

Surgery 1995

Focused observational studies done DG SICU patients

Early Neutrophil Sequestration after Injury: A Pathogenic Mechanism for Multiple Organ Failure

Abraham J. Botha, MD, Frederick A. Moore, MD, Ernest E. Moore, MD, Angela Sauaia, MD, Anirban Banerjee, PhD, and Verlyn M. Peterson, MD

J Trauma 1995

After 72 hours circulating PMN's are non-responsive

Printed in the U.S.A.

Multiple Organ Failure Can Be Predicted as Early as 12 Hours after Injury

Angela Sauaia, MD, PhD, Frederick A. Moore, MD, Ernest E. Moore, MD, Jill M. Norris, PhD, Dennis C. Lezotte, PhD, and Richard F. Hamman, MD, DrPH

J Trauma 1998

Angela Sauaia

Denver MOF Database

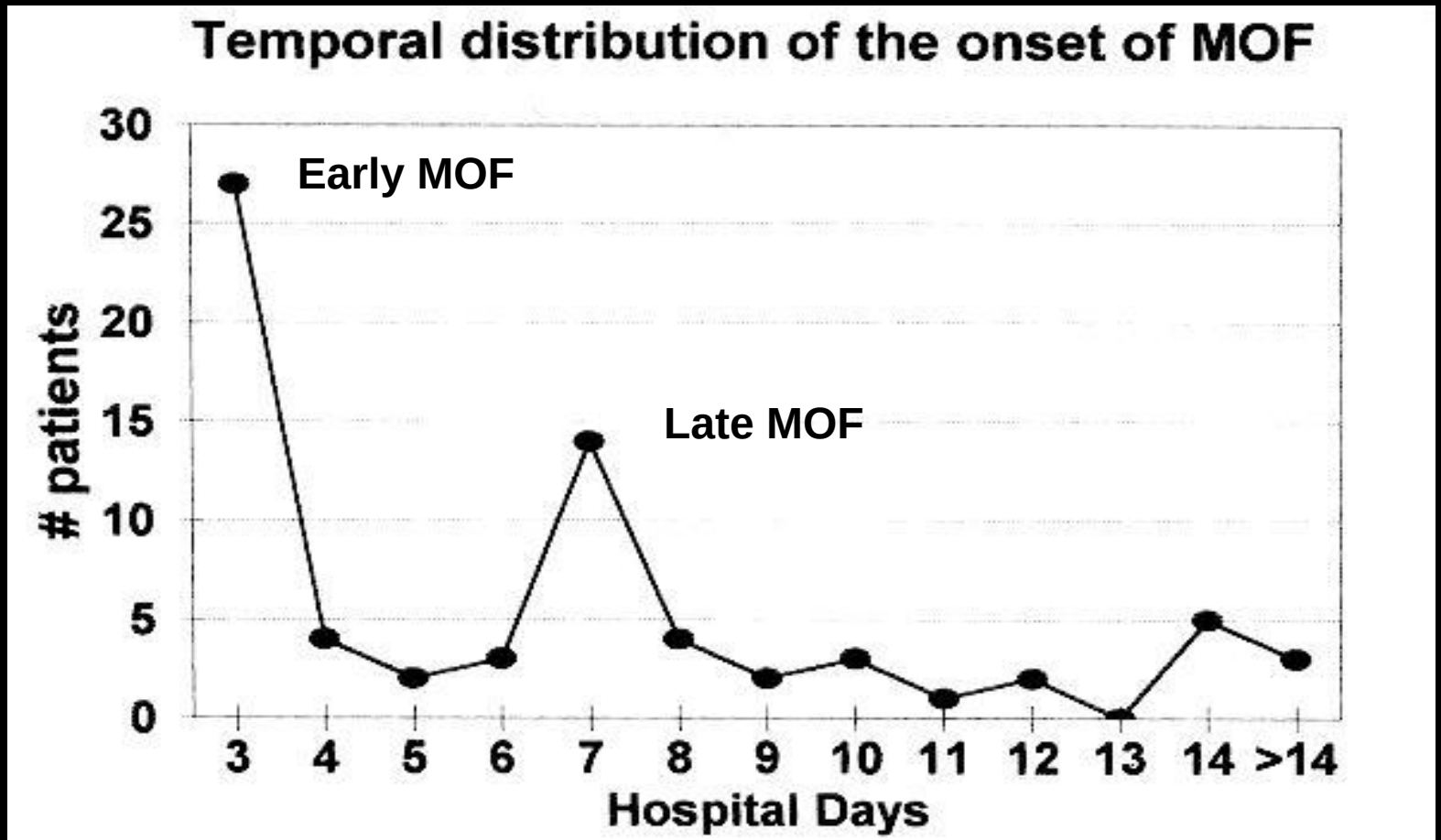
- Denver MOF Score
- Defined Clinical Dataset to Study MOF
- Linked to Research Data

Postinjury Multiple Organ Failure: A Bimodal Phenomenon

Frederick A. Moore, MD, Angela Sauaia, MD, Ernest E. Moore, MD, James B. Heanel, RRT, Jon M. Burch, MD and Dennis C. Lezotte, PhD

J Trauma 1996

Denver MOF Database



Cartoon # 4

Dysfunctional Inflammatory Response

Shock

Severe SIRS

Moderate SIRS

Early MOF

Moderate Immunosupression

Severe Immunosupression

Innate Immunity

Neutrophils

Infections → Late MOF

Immunologic Dissonance: A Continuing Evolution in Our Understanding of the Systemic Inflammatory Response Syndrome (SIRS) and the Multiple Organ Dysfunction Syndrome (MODS)

Roger C. Bone, MD

Ann Intern Med 1996

Roger Bone

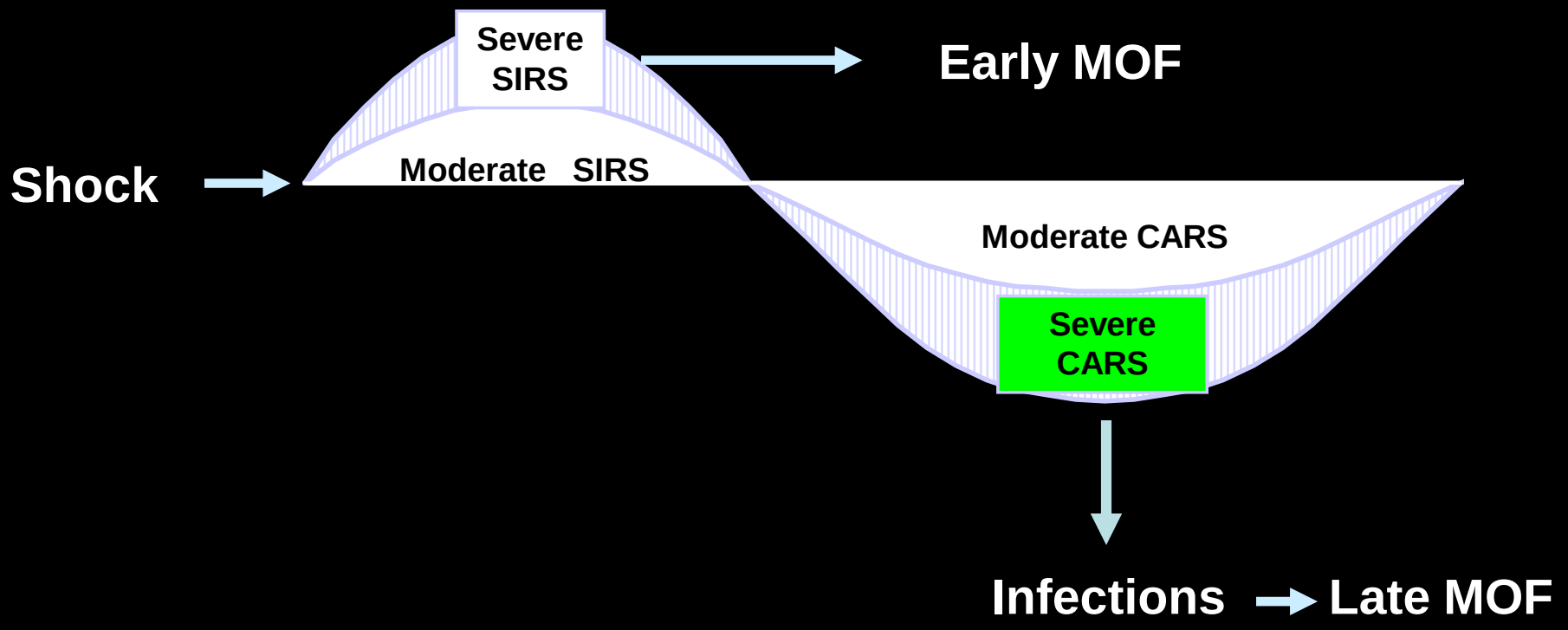
Adaptive Immune Response
Lymphocytes

CARS

Compensatory Anti-inflammatory Response Syndrome

New Paradigm

Immunologic Trajectory of a Complicated ICU Course



Adaptive Immunity Changes that Characterize CARS

Increased Tregs	Monneret, G, Debard, AL, Venet, F, et al., *Marked elevation of human circulating CD4+CD25+ regulatory T cells in sepsis-induced immunoparalysis.* Crit Care Med, 2003. 31(7): p. 2068-71.
T cell anergy	Bone, RC. Sir Isaac Newton, sepsis, SIRS, and Cars. *Crit Care Med*, 1996 24(7): p.1125-8.
Shift from THI to TH2 phenotype	Delano, MJ, Scumpia, PO, Weinstein, JS, et al., *MyD88-dependent expansion of an immature GR-1(+)CD11b(+) population induces T cell suppression and Th2 polarization in sepsis.* J Exp Med, 2007. 204(6): p. 1463-74.
Macrophage Paralysis **-*decreased cytokine production*** **-*decreased bacterial clearance*** **- *decreased antigen presentation***	Munoz, C, Carlet, J, Fitting, C, et al., *Dysregulation of in vitro cytokine production by monocytes during sepsis.* J Clin Invest, 1991. 88(5): p. 1747-54 Ayala, A and Chaudry, IH, *Immune dysfunction in murine polymicrobial sepsis: mediators, macrophages, lymphocytes and apoptosis.* Shock, 1996. 6 Suppl 1: p. S27-38
Lymphocyte Apoptosis	Hotchkiss, R. S., Swanson, P. E., Cobb, J. P. et al. Apoptosis in lymphoid and parenchymal cells during sepsis: findings in normal and T- and B-cell-deficient mice. *Crit Care Med, 1997* 25(8): p. 1298-1307.
Suppressed T cell proliferation	De Waal Malefyt R, Haanen J, Spits H, et al: Interleukin 10 (IL-10) and viral IL-10 strongly reduce antigen-specific human T cell proliferation by diminishing the antigen-presenting capacity of monocytes via downregulation of class II major histocompatibility complex expression. J Exp Med 1991; 174:915-924

University of Colorado Trauma Research Center

Alden Harken

Where I learned “ Team Science ”

Rich Andrassy

New Chairman
1995

UT★HOUSTON
MEDICAL SCHOOL

Hermann Hospital

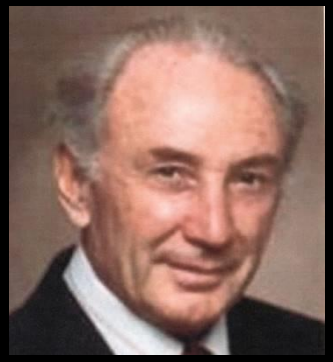
UT - Houston

Recruited Me

Medical Director Trauma & Chief of General Surgery

NIGMS Sponsored P-50 Trauma Center Grant
Sepsis Induced Ileus

Frank Moody



Program Director

Decreased ileal muscle contractility and increased **iNOS** expression induced by lipopolysaccharide

NORMAN W. WEISBRODT, THOMAS A. PRESSLEY, YONG-FANG LI, MALGORZATA J. ZEMBOWICZ, SANDRA C. HIGHAM, ARTUR ZEMBOWICZ, ROBERT F. LODATO, AND FRANK G. MOODY

Am J Physiology 1996

Scott Somers*

It's not an Entitlement Program

P50 Programs Need to Evolve

* **New NIGMS P50 Program Officer**

Inducible Nitric Oxide Synthase Mediates Gut Ischemia/Reperfusion-Induced Ileus Only after Severe Insults[1]

Heitham T. Hassoun, M.D.,* Norman W. Weisbrodt, Ph.D.,† David W. Mercer, M.D.,* Rosemary A. Kozar, M.D., Ph.D.,* Frank G. Moody, M.D.,* and Frederick A. Moore, M.D.*,[2]

Molecular regulation of gut I/R induced ileus

Heitham Hassoun

1St UT-Houston Research Fellow

“Diamond in the Rough”

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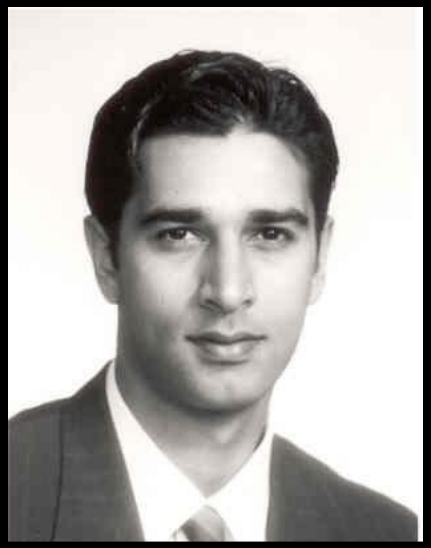
Molecular regulation of gut I/R induced ileus

Heitham Hassoun



1St UT-Houston Research Fellow

Denver SMAO rodent model

Dr Moody's intestinal transit model

iNOS induced gut inflammation

Novel iNOS blockers

Nitric Oxide

Ferid Murad lab

Create Relevant Lab Model

POST-INJURY MULTIPLE ORGAN FAILURE: THE ROLE OF THE GUT

Heitham T. Hassoun,* Bruce C. Kone,† David W. Mercer,* Frank G. Moody,*
Norman W. Weisbrodt,‡ and Frederick A. Moore*

Department of Surgery, †Division of Nephrology, Department of Medicine, ‡Department of Integrative Biology, Pharmacology, and Physiology, University of Texas-Houston Medical School, Houston, Texas 77030

Wrote a Review Articles

Our " Story of Life "

Research Focus: Role of the gut in MOF

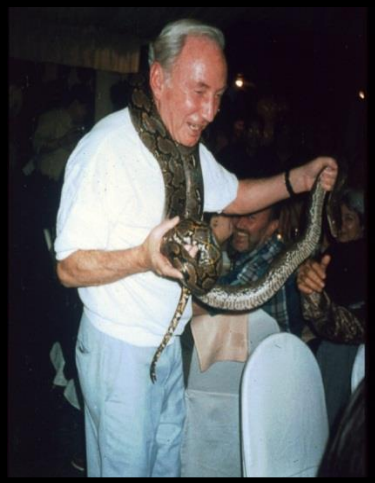
POST-INJURY MULTIPLE ORGAN FAILURE: THE ROLE OF THE GUT

Heitham T. Hassoun,* Bruce C. Kone,† David W. Mercer,* Frank G. Moody,* Norman W. Weisbrodt,‡ and Frederick A. Moore*

*Department of Surgery, †Division of Nephrology, Department of Medicine, ‡Department of Integrative Biology, Pharmacology, and Physiology, University of Texas-Houston Medical School, Houston, Texas 77030

Bruce Kone
Chair of Medicine

David Mercer
Chief LBJ

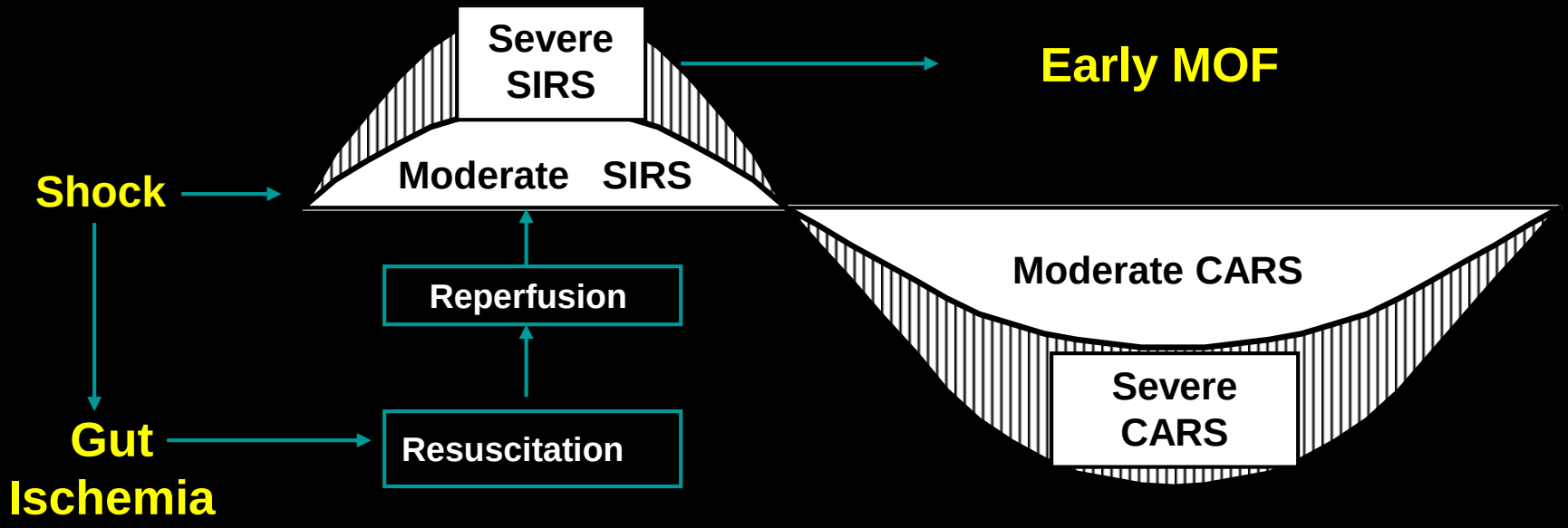


Frank Moody
PD of P 50 grant

Norm Weisbrodt
Chair of Physiology

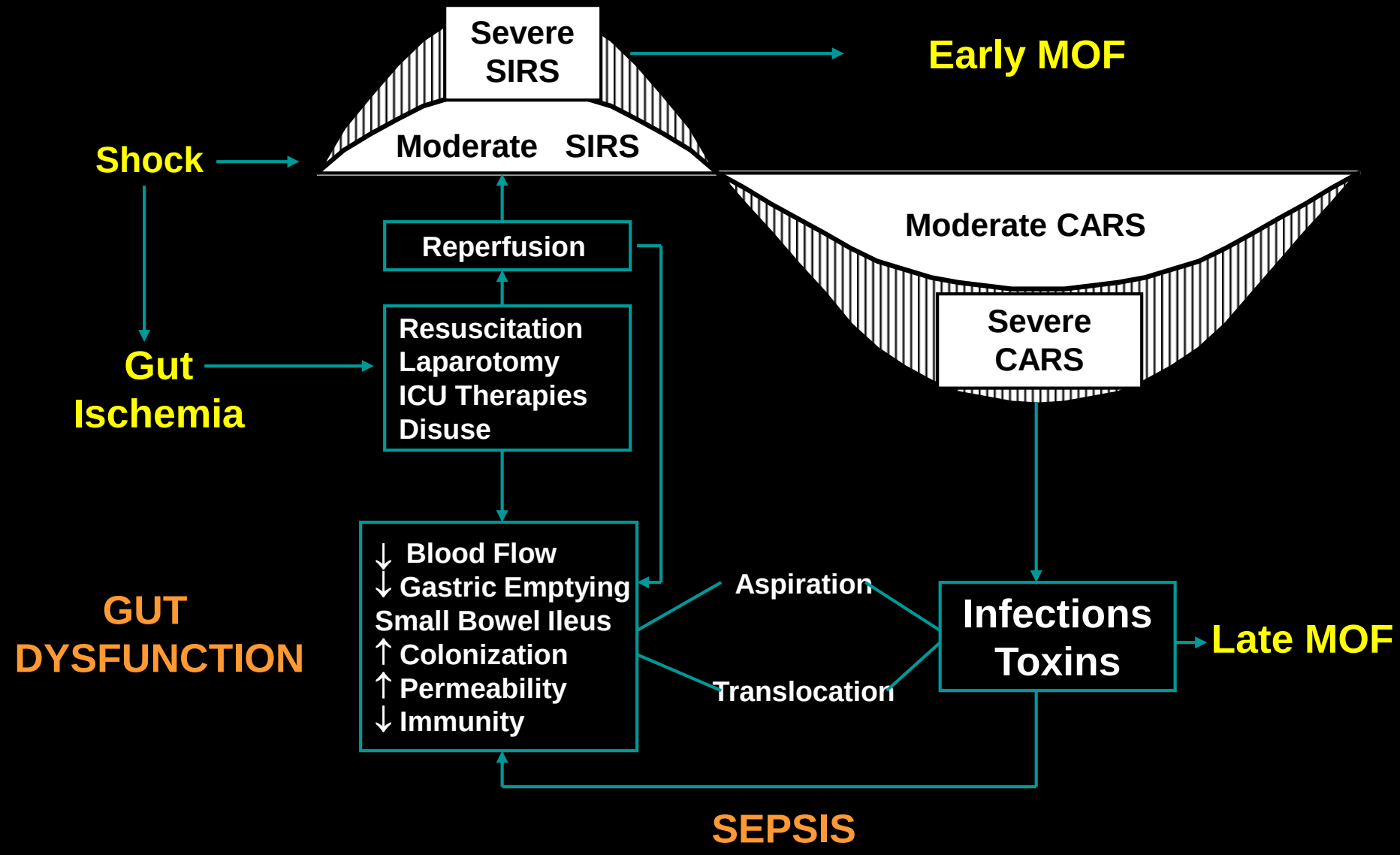
Aligned These Institutional “Super Stars”

GUT IS THE INSTIGATOR & VICTIM OF THIS RESPONSE



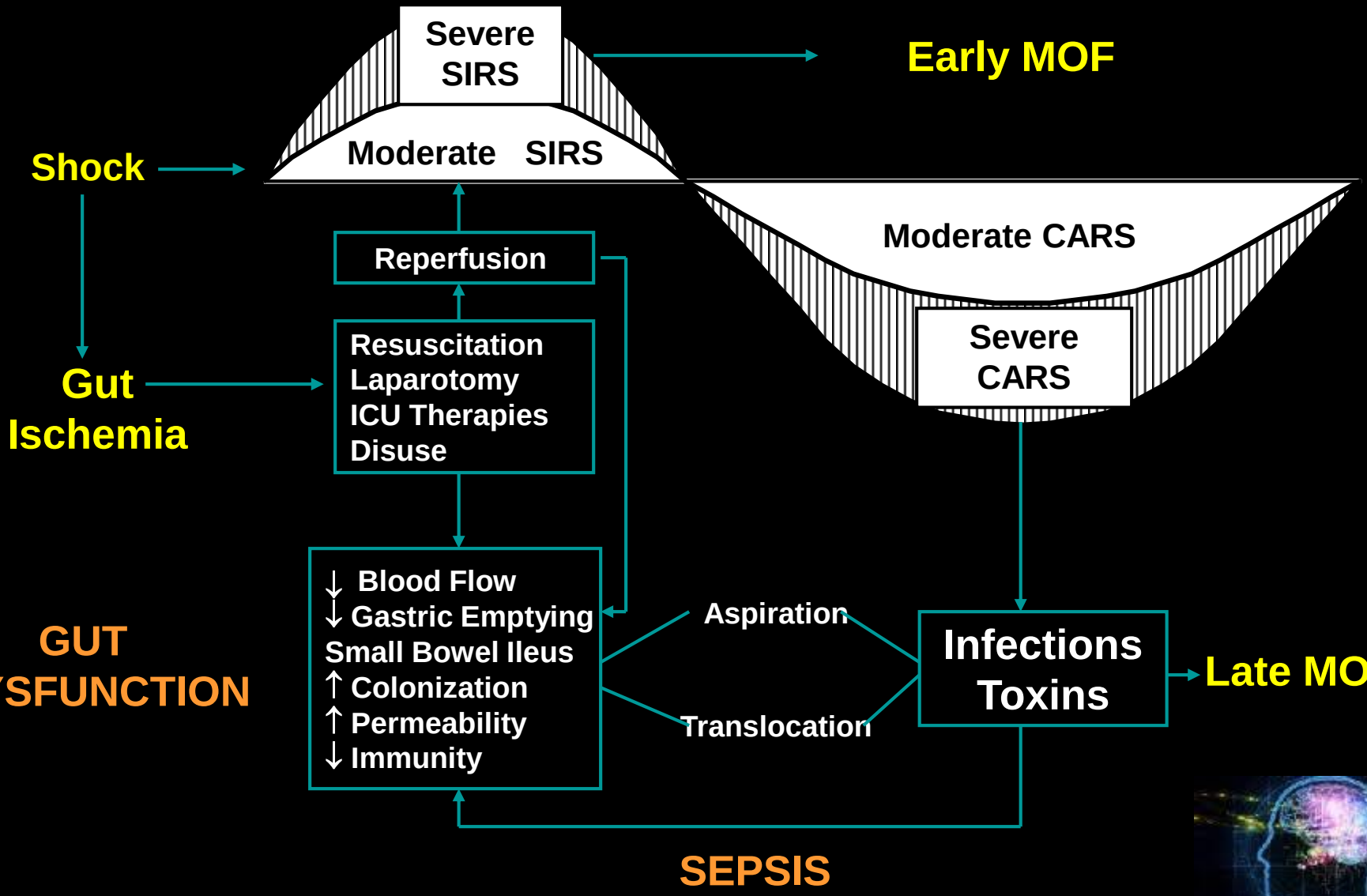
Lipid Mediators in Mesenteric Lymph

GUT IS THE INSTIGATOR & VICTIM OF THIS RESPONSE

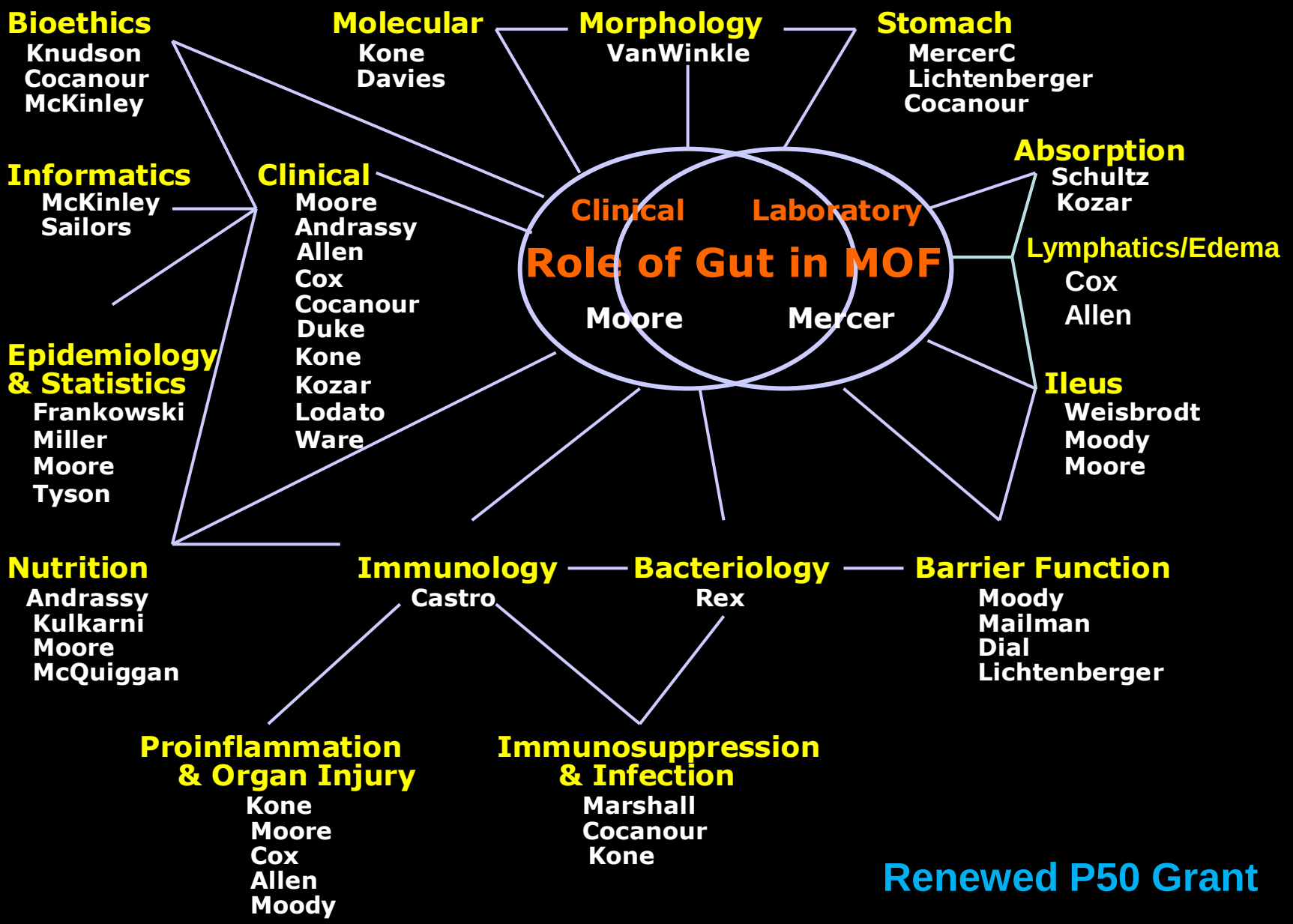


Cartoon # 5

GUT IS THE INSTIGATOR & VICTIM OF THIS RESPONSE



TRAUMA RESEARCH CENTER



Renewed P50 Grant

Where I learned develop & implement a team science program

Ron Tompkins

Glue Grant

INFLAMMATION & the Host Response to Injury

Inflammation and the Host Response to Injury

NIGMS U54 Grant $ 100 million

8 US Trauma Centers (5 had P50 grants)

Purposes

1) Develop and validate genomic assays in blood

2) Document the genomic response after severe trauma

3) Test the SIRS/CARS hypothesis

Inflammation and the Host Response to Injury
Patient-Oriented Research Core
Standard Operating Procedures for Clinical Care

Ronald V. Maier, MD, Paul Bankey, MD, PhD, Bruce McKinley, PhD, Brad Freeman, MD,
Brian G. Harbrecht, MD, Jeffrey L. Johnson, MD, Joseph P. Minei, MD, Ernest E. Moore, MD,
Fredrick Moore, MD, Avery B. Nathens, MD, PhD, MPH, Michael Shapiro, MD,
Ronald G. Tompkins, ScD, MD, Michael West, MD, PhD,
and the Inflammation and the Host Response to Injury Investigators

***J Trauma* 2005**

Developed Standard Operating Procedures for ICU Care

- Shock resuscitation
- Mechanical ventilation and weaning
- Venous thromboembolism prophylaxis
- Stress Gastritis Prophylaxis
- Prevention, diagnosis and treatment of VAP
- Strict glycemic control
- Nutritional support
- Transfusion
- Sedation and analgesia

INFLAMMATION & the Host Response to Injury

Benchmarking Outcomes in Critically Injured Trauma Patients

Joseph Cuschieri, MD; Jeffery L.Johnson, MD;Jason Sperry, MD; Michael A. West, M, PhD; Ernest E. Moore, MD; Joseph P.Minei, MD; et.al and the Inflammation and Host Response to Injury Large Scale Collaborative Research Program.

Ann Surg 2012

~30% Incidence MOF, but Late MOF Deaths Disappeared

The Changing Pattern and Implications of Multiple Organ Failure after Blunt Injury With Hemorrhagic Shock

Joseph P.Minei, MD; Joseph Cuschieri, MD; Jason Sperry, MD; Ernest E. Moore, MD; Michael A. West, MD, PhD; Brian G. Harbrecht, MD; Grant E. O'Keefe, MD; Mitchell J. Cohen, MD; Lyle L. Moldawer, PhD; Ronald Tompkins, MD, ScD; Ronald V. Maier, MD; the Inflammation and the Host Response to Injury Collaborative Research Program

Crit Care Med 2012

INFLAMMATION & the Host Response to Injury

The Methodist Hospital (TMH), Houston TX

Sepsis in major killer in surgical ICU

Chief of Acute Care Surgery 2006 - 2011

Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

R. Phillip Dellinger, MD; Jean M. Carlet, MD; Henry Masur, MD; Herwig Gerlach, MD, PhD; Thierry Calandra, MD; Jonathan Cohen, MD; Juan Gea-Banacloche, MD, PhD; Didier Keh, MD; John C. Marshall, MD; Margaret M. Parker, MD; Graham Ramsay, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; Mitchell M. Levy, MD; for the Surviving Sepsis Campaign Management Guidelines Committee

Crit Care Med 2004

Wonderful Contribution ! - Implementation is Challenging

Early Diagnosis of Sepsis is Difficult

Difficult to Remember & Prioritize the Recommendations

Validation of a Screening Tool for the Early Identification of Sepsis

Laura J. Moore, MD, Stephen L. Jones, MD, Laura A. Kreiner, MD, Bruce McKinley, PhD, Joseph F. Sucher, MD, S. Rob Todd, MD, Krista L. Turner, MD, Alicia Valdivia, RN, and Frederick A. Moore, MD

J Trauma 2009

Developed Sepsis Screening Tool and

Computerized Clinical Decision Support (CDDS) Protocol

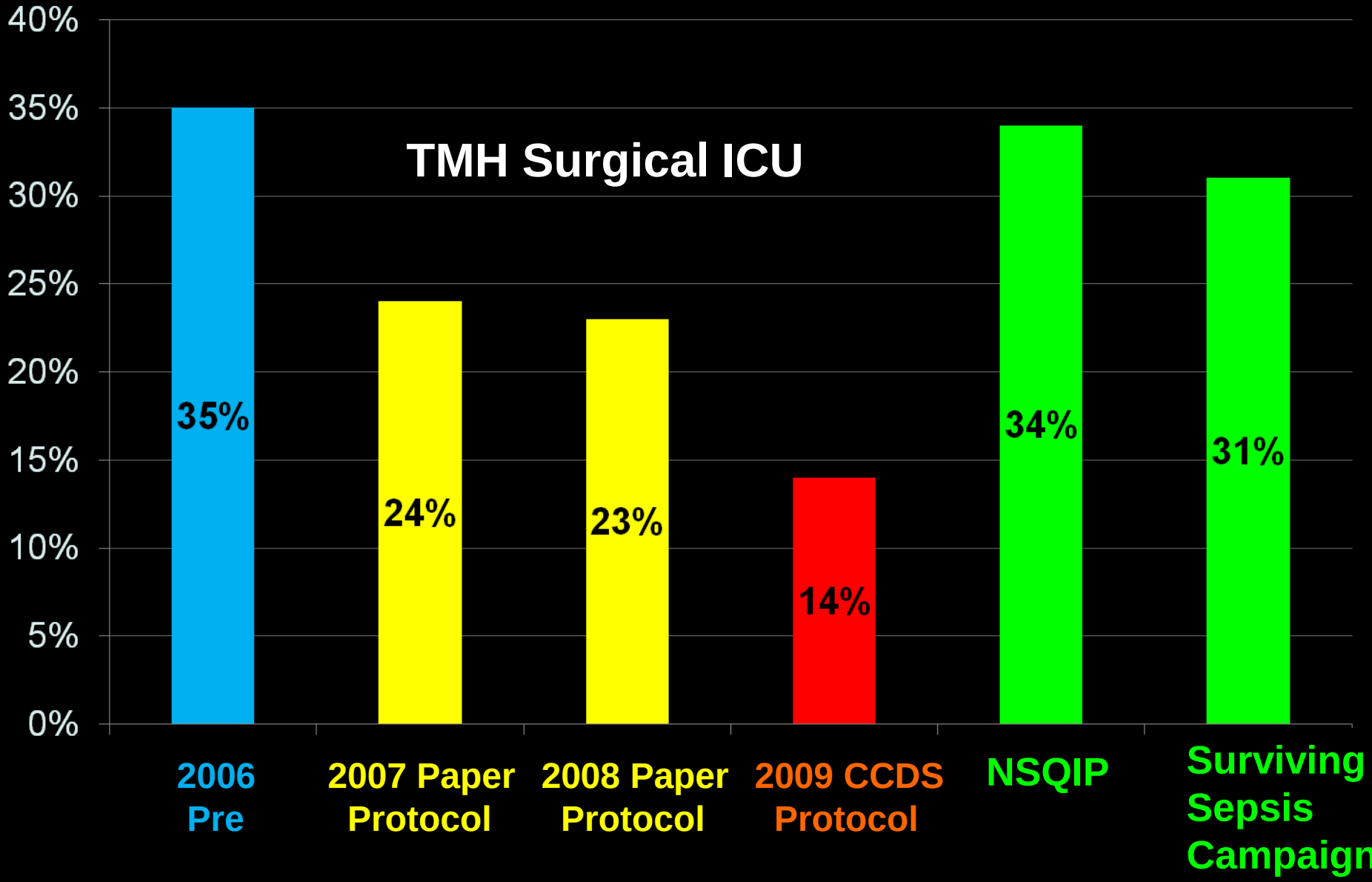
Computer Protocol Facilitates Evidence Based Care of Sepsis in the Surgical Intensive Care Unit

Bruce A. McKinley, PhD, Laura J. Moore, MD, Joseph F. Sucher, MD, Rob Todd, MD
Krista L. Turner, MD, Alicia Valdivia, RN, Matthew Sailors, BE and Frederick A. Moore MD

J Trauma 2011

Data Collected by Hospital PI

% MORTALITY
Severe Sepsis/Septic Shock



The Epidemiology of Sepsis in General Surgery Patients

Laura J. Moore, MD, Bruce A. McKinley, PhD, Krista L. Turner, MD, Rob Todd, MD
Joseph F. Sucher, MD, Alicia Valdivia, RN, Matthew Sailors, BE, Lillian S. Kao, MD
and Frederick A. Moore MD

J Trauma 2011

Only 25 % of sepsis survivors were discharged to **home**

UF UNIVERSITY of FLORIDA

Chief of Acute Care Surgery

July 2011

Lyle Moldawer PhD

laboratory of Inflammation Biology and Surgical Science

University of Florida College of Medicine

UF Basic Scientist X 25 yrs

Stress Metabolism

Cytokine Storm

Characterize CARS

Glue Grant

Build a Translational Research Program

Obtain a NIGMS P50 "Team Science" Grant

Reorganized Surgical and Trauma ICUs

Intensivist Led Multidisciplinary ICU teams

Evidence Based Protocols

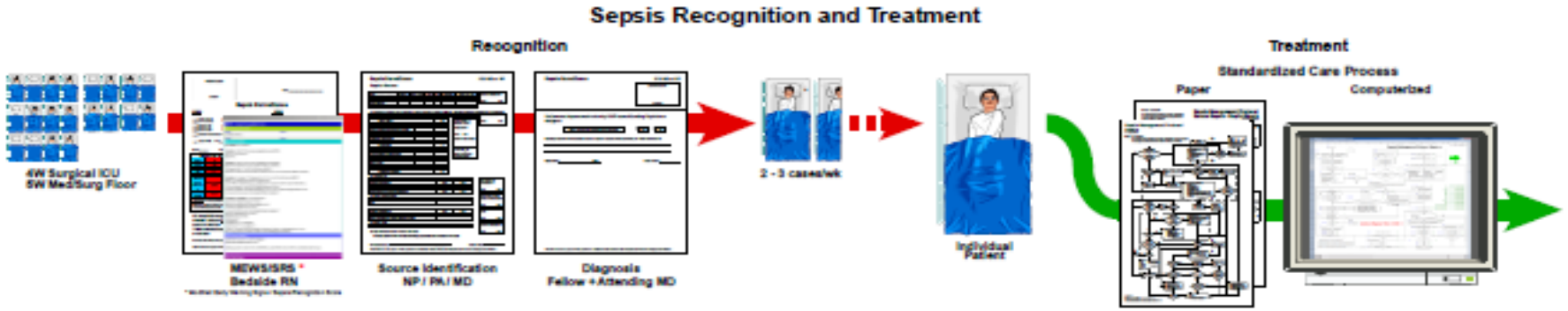
Sedation, analgesia & delirium
TBI management
Mechanical ventilation and ARDS alternatives
Sedation holidays and daily SBTs
Prevention, diagnosis and treatment of VAP
Shock resuscitation
Stress Gastritis Prophylaxis
Nutritional support
Glycemic control
Electrolyte replacement
Restrictive transfusion
DVT prophylaxis
Sepsis Screening and Early Management

UF UNIVERSITY of FLORIDA College of Medicine

Got Sepsis?
A Process for Improving Recognition and Treatment of Sepsis

Victoria Klink, Peggy S. Marker, Philip A. Efron, R. Matthew Sailors, Bruce A. McKinley, Frederick A. Moore

Shands Experienced Care Expert Caring



Computer versus paper system for recognition and management of sepsis in surgical intensive care

Chasen A. Croft, MD, Frederick A. Moore, MD, Philip A. Efron, MD, Peggy S. Marker, MSN, Andrea Gabrielli, MD, Lynn S. Westhoff, BSN, Lawrence Lottenberg, MD, Janeen Jordan, MD, Victoria Klink, BSN, R. Matthew Sailors, BE, *and* Bruce A. McKinley, PhD, *Gainesville, Florida*

2013 AAST Plenary Paper

J Trauma Acute Care Surgery 2014

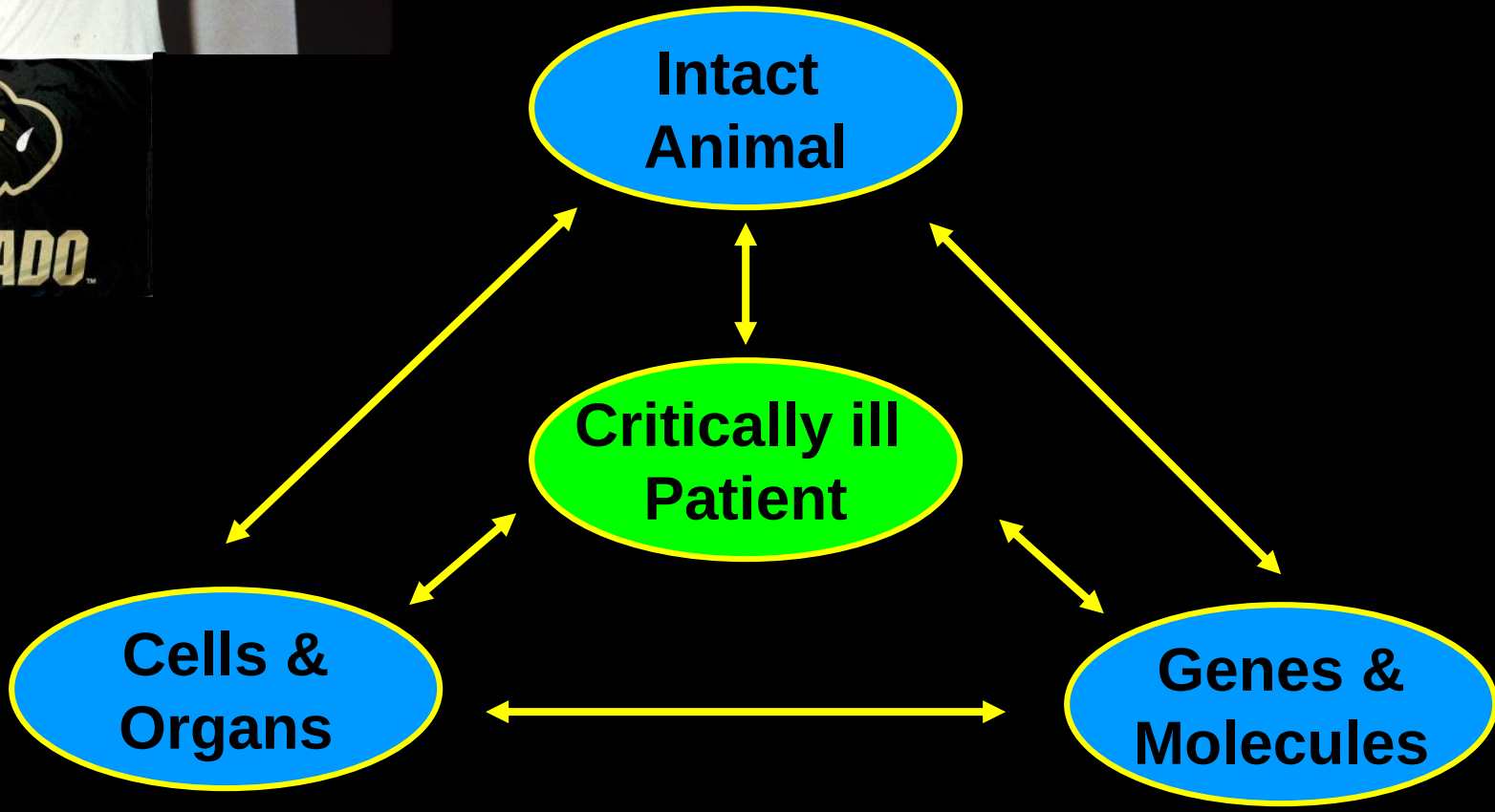
Mortality of Severe Sepsis/Septic Shock

28% ⟶ 14 %

Alden Harken

Study Your Patients!

TRANSLATIONAL RESEARCH



New Chronic Critical Illness (CCI) MOF Phenotype

Prolonged ICU stays - manageable organ dysfunction

Recurrent inflammatory insults & nosocomial infections

Persistent acute phase response - very high CRPs

Neutrophilia and lymphopenia

Cachexia despite good nutrition - a wasting disease like cancer

Poor wound healing & decubitus ulcers

Transfer to LTACs for indolent death

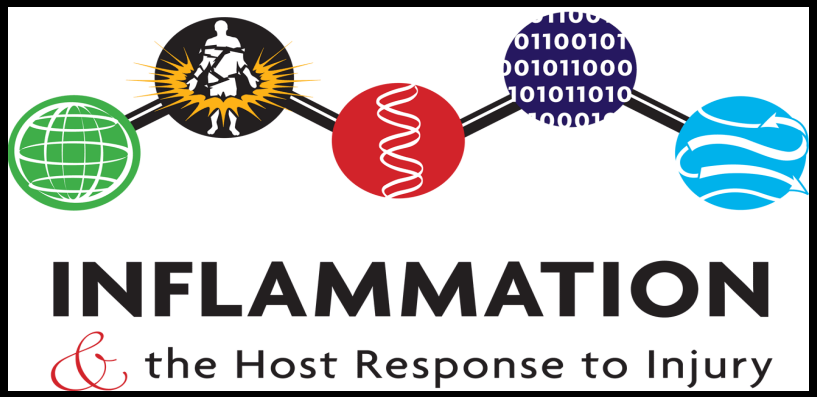
Sepsis recidivism

A genomic storm in critically injured humans

Wenzhong Xiao, Michael N. Mindrinos, Junhee Seok, Joseph Cuschieri, Alex G. Cuenca, Hong Gao, and the Inflammation and Host Response to Injury Large-Scale Collaborative Research Program

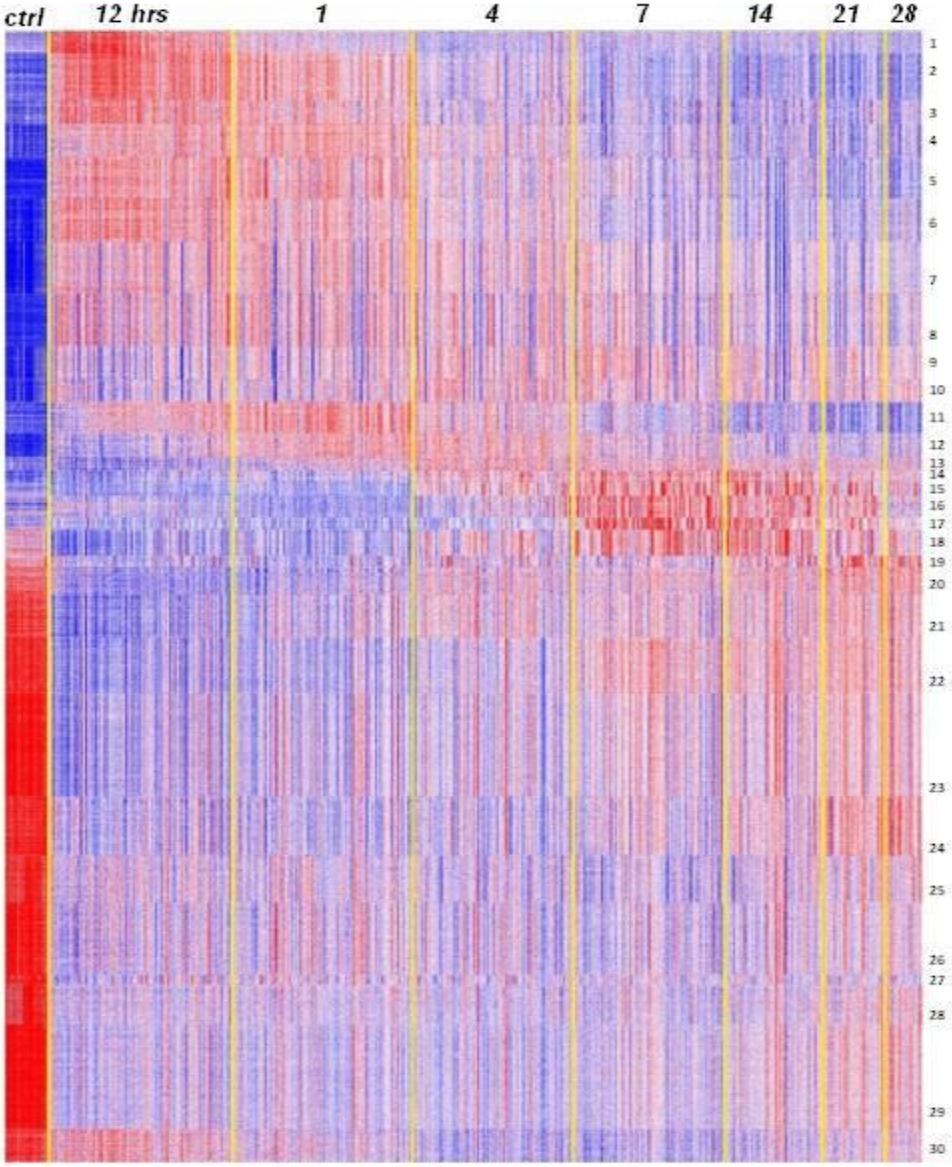
J. Exp. Med 2012

Glue Grant

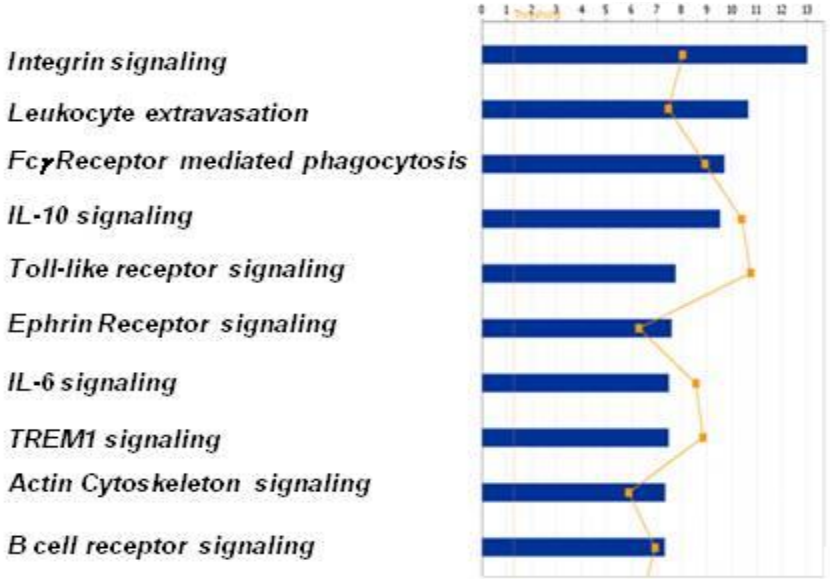


A Genomic Storm – 75% of Genes Up or Down Regulated

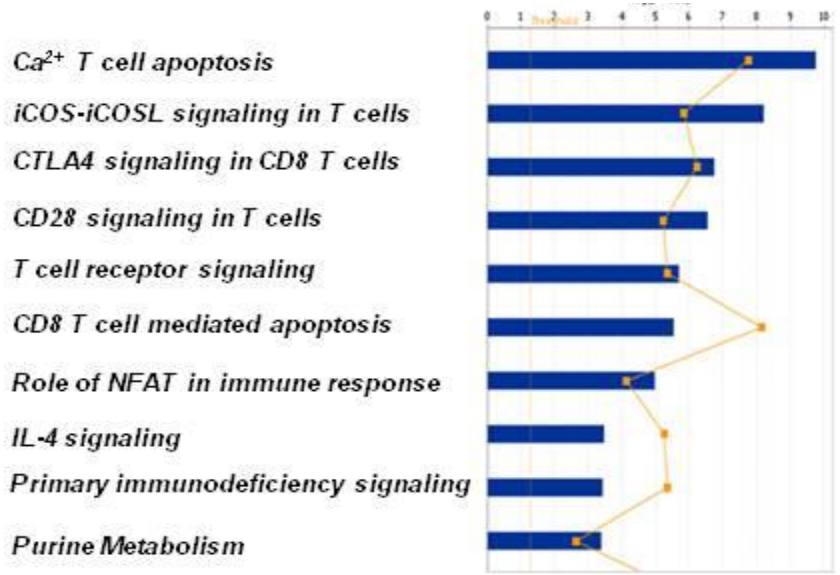
A. Gene expression After Severe Trauma



B. Up-regulated Innate Immunity

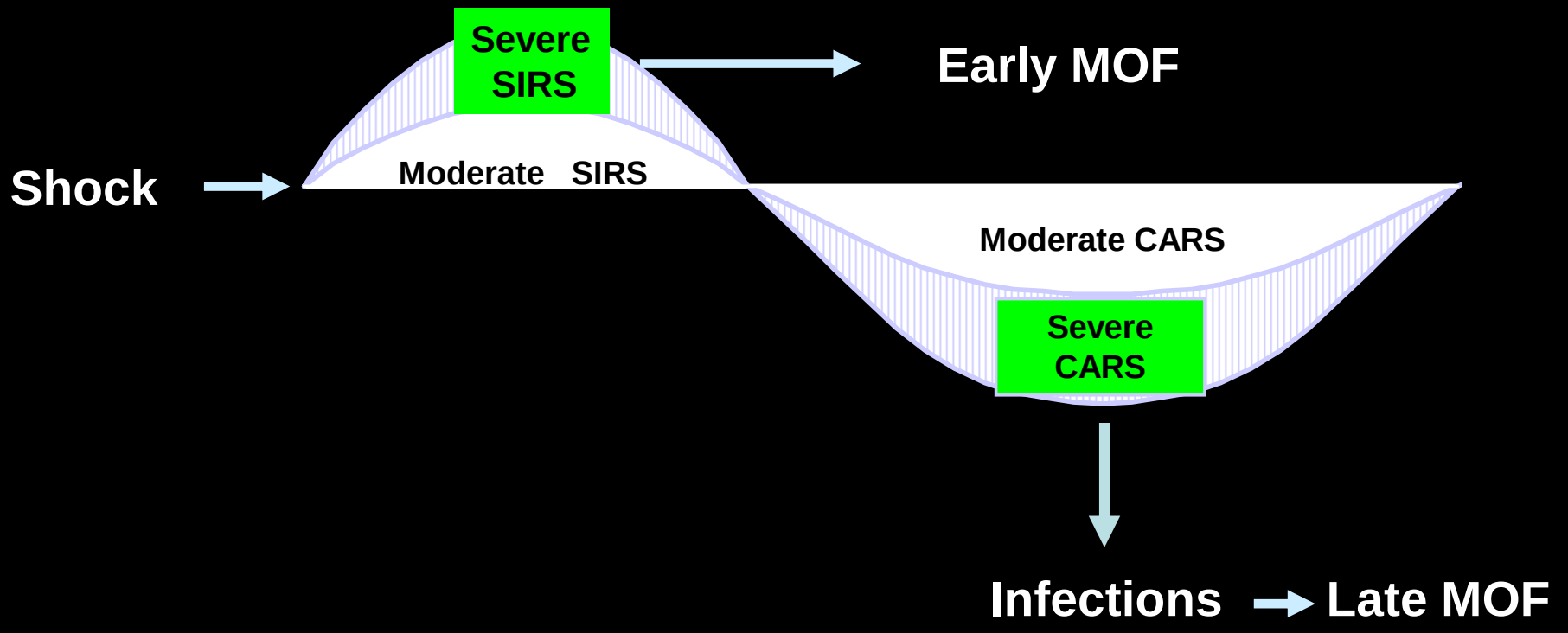


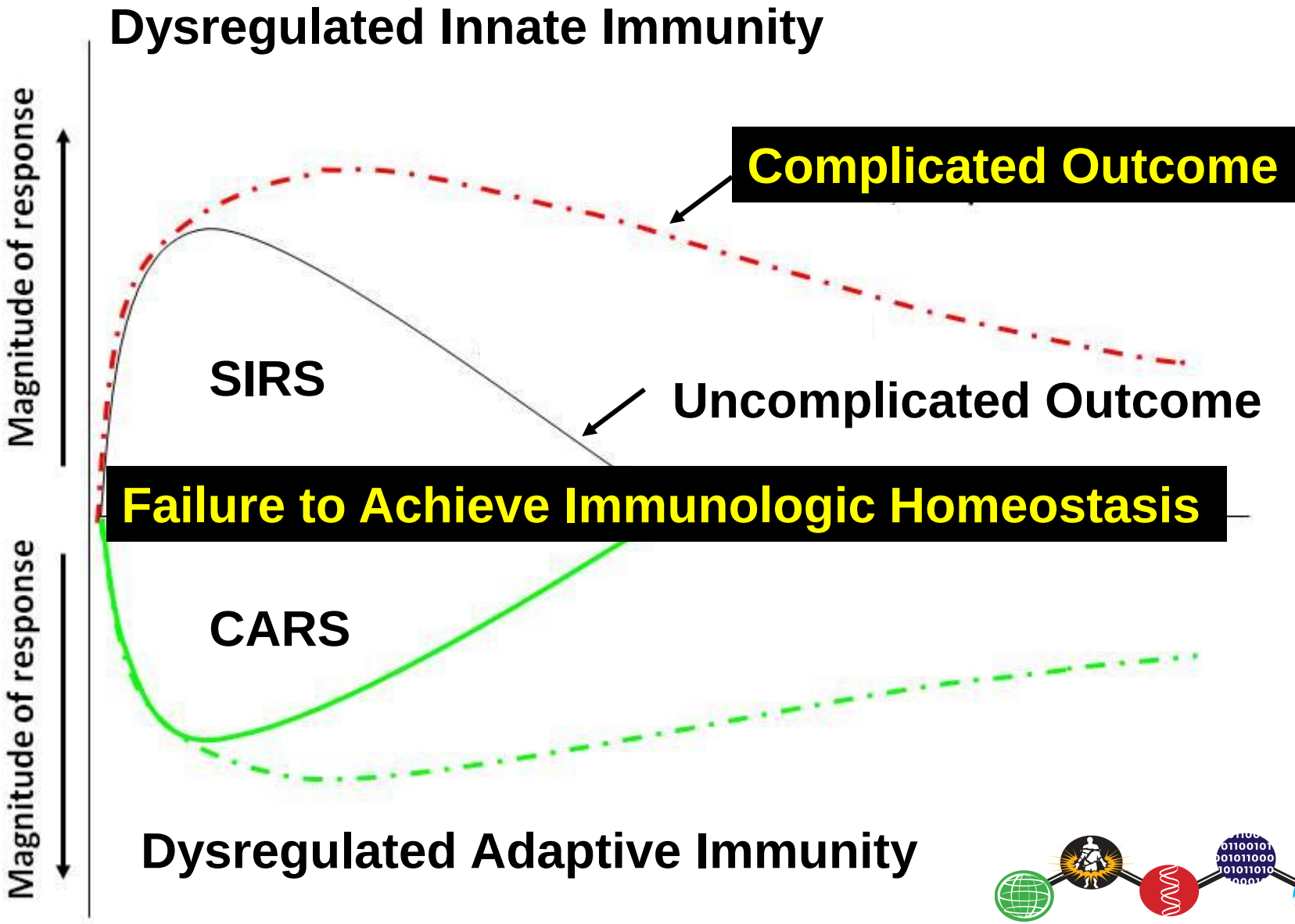
C. Down-regulated Adaptive Immunity

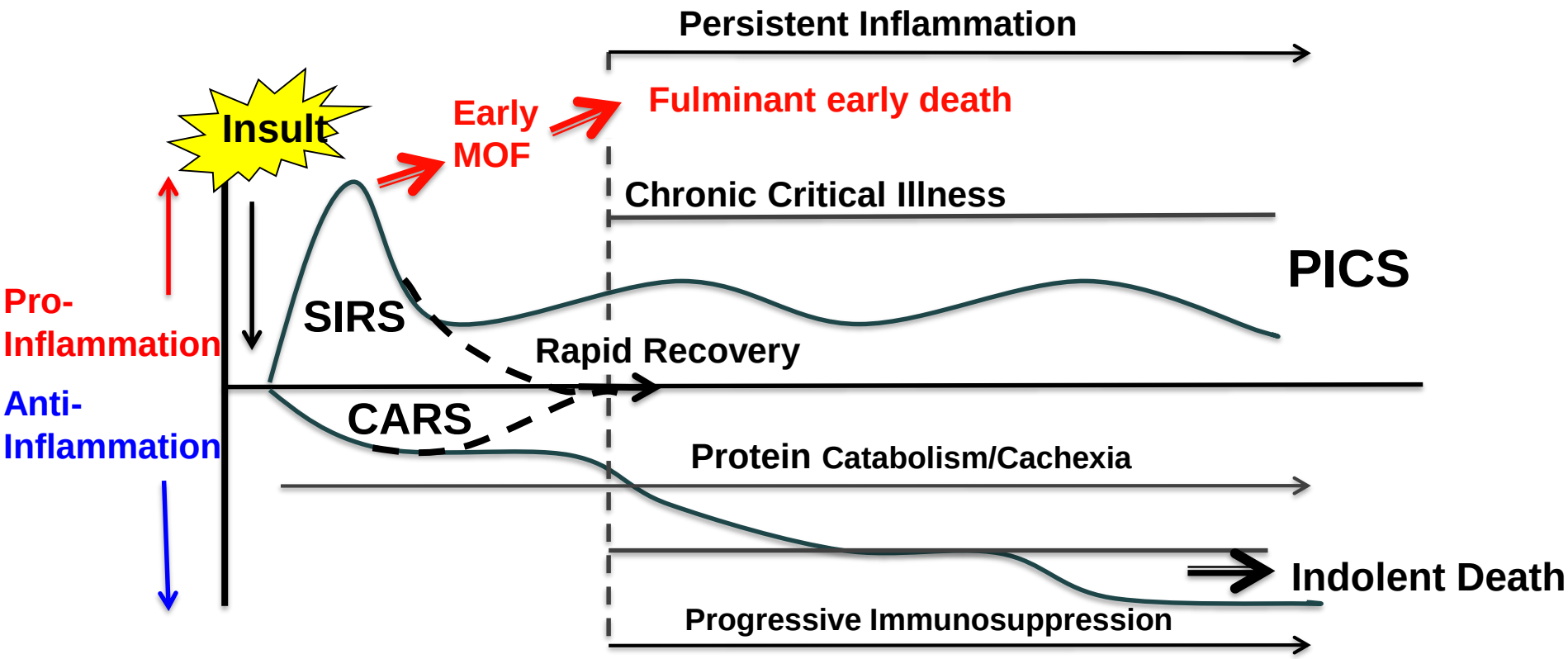


Study Hypothesis

Immunologic Trajectory of a Complicated ICU Course







Wrote a Review Article

Persistent inflammation and immunosuppression: A common syndrome and new horizon for surgical intensive care

Lori F. Gentile, MD, Alex G. Cuenca, MD, PhD, Philip A. Efron, MD, Darwin Ang, MD, PhD, MPH, Azra Bihorac, MD, Bruce A. McKinley, PhD, Lyle L. Moldawer, PhD, *and* Frederick A. Moore, MD, *Gainesville, Florida*

J Trauma 2012

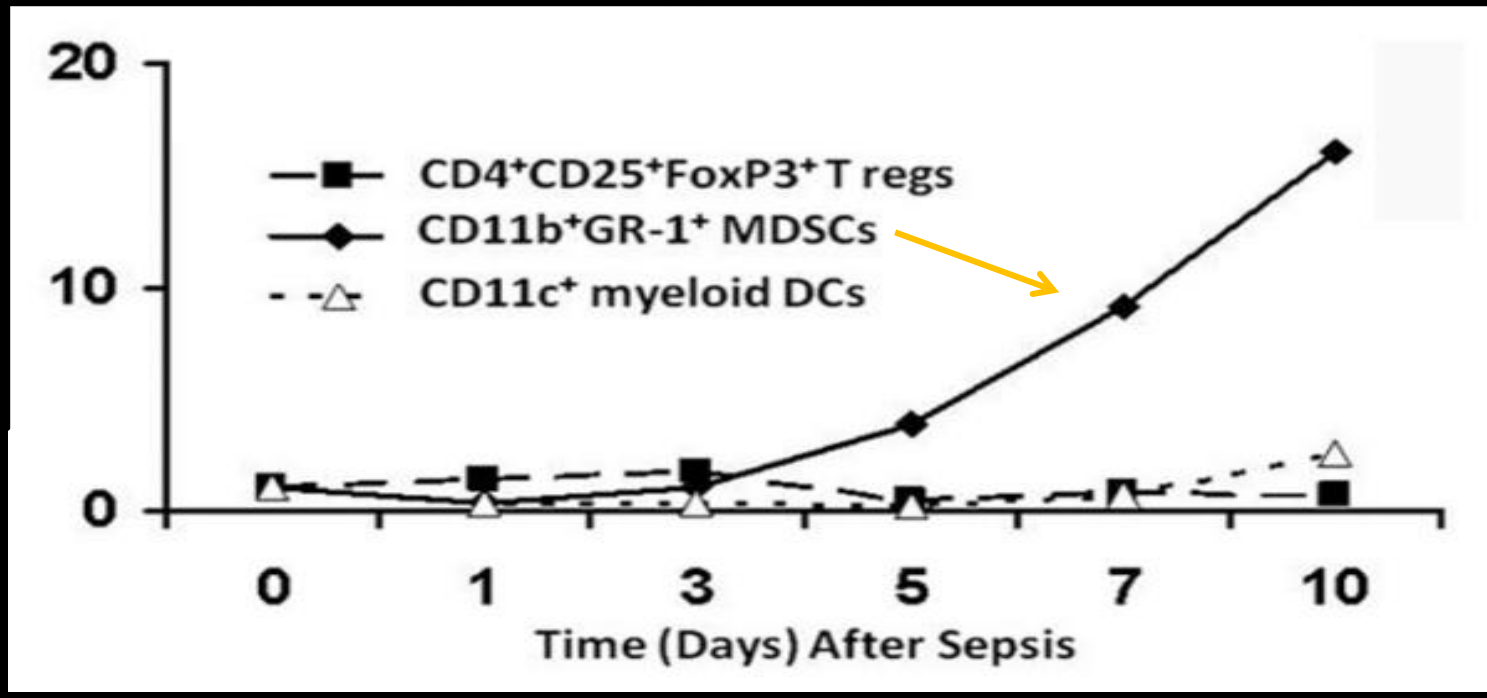
A Paradoxical Role for Myeloid-Derived Suppressor Cells In Sepsis and Trauma

Alex G Cuenca, Matthew J Delano, Kindra M. Scumpia, Claudia Moreno, Phillip O Scumpia, Drake M LaFace, Philip A Efron and Lyle L Moldawer

Mol Med 2011

T32 Fellow

MDSC Expansion in Chronic CLP Sepsis Model



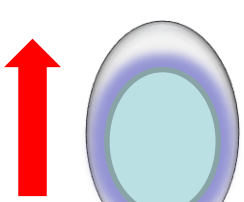
Conserved Bone Marrow Response to a Variety of Insults

Emergency Myelopoesis

Injury
Infection
Tumor Growth
Inflammation

Promote Innate Immunity

Hemopoeitic Stem Cells



Myeloid Progenitors

Myeloid Derived Suppressor Cells

Suppress Adaptive Immunity

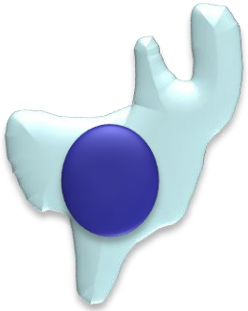
Lymphoid Progenitors

Lymphopenia

Released Early from Bone Marrow

Granulocytes

Macrophages



Dendritic Cells

Myeloid Derived Suppressor Cells (MDSCs)

Fight infections (but are poor phagocytes)

Cause inflammation (via NO, MPO & ROS)

Cause immunosuppression: ↓ Antigen presentation
↓ T-cell proliferation
↑ anti-inflammatory cytokines

Impair wound healing: express arginase-1,depletes arginine

Cartoon # 6

A. Clinical Response

Early Innate immunity

Persistent Inflammation

Sepsis

Early MOF

Fulminant death

Chronic Critical Illness

PICS

Pro-Inflammation

SIRS

Rapid Recovery

Anti-Inflammation

CARS

Protein Catabolism/Cachexia

Indolent Death

Driving Mechanism

B. Individual Cell Response

Moldawer Lab Studies

Macrophage Activation

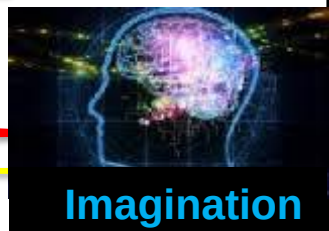
MDSCs

TRegs

Dendritic Cells

Macrophage Paralysis

T Effector Cell Number and Function



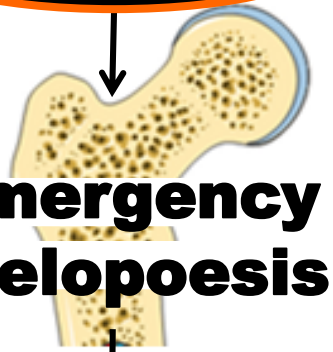
Project 1

PICS-CCI Phenotype

Cechexia & Malnutrition
Chronic Kidney Insufficiency
Poor Vascular Health
Ventilator Dependence
↓ Ability to Carry-out AODLs
Poor Wound Healing
↑ Long-term Mortality
Failure to Rehabilitate
Indolent death

Long Term Effects of CCI

Sepsis



Emergency Myelopoesis

Sepsis Recidivism

Project 2

Beneficial Effects of MDSCs

Improved Immune Surveillance:
- ↑ NO, ROS, & Phagocytosis
Accentuate Acute Inflammation

CCI Progression

Project 4

↓ Nutrient Utilization
Loss of Lean Muscle Mass
↑ Nosocomial Infections
Ventilator Dependence
↓ Adaptive Immunity
Delirium and ↓ Mobility

Pathway to PICS-CCI

AKI

No AKI

Project 3

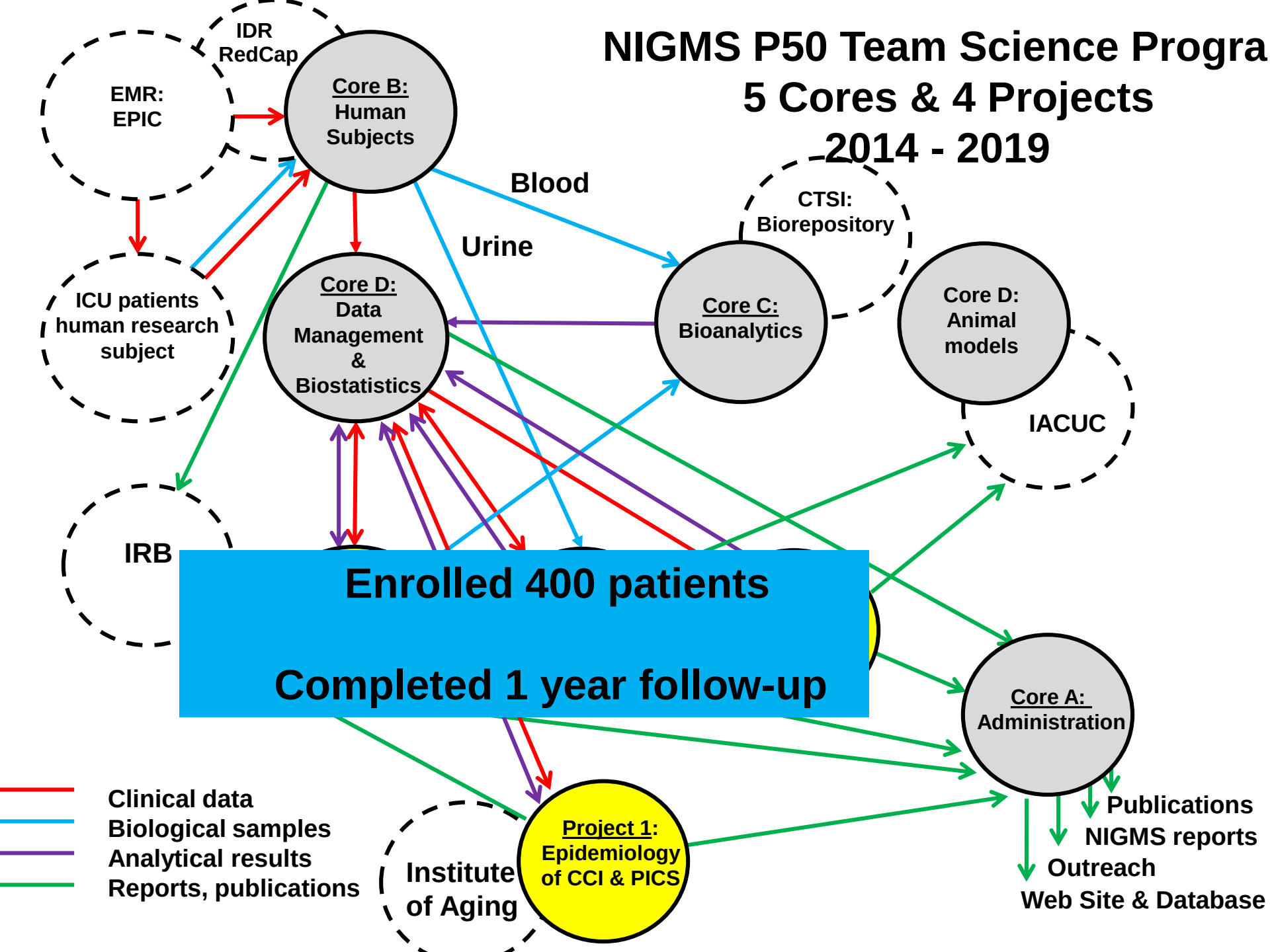
Rapid Recovery

Short Term Consequences

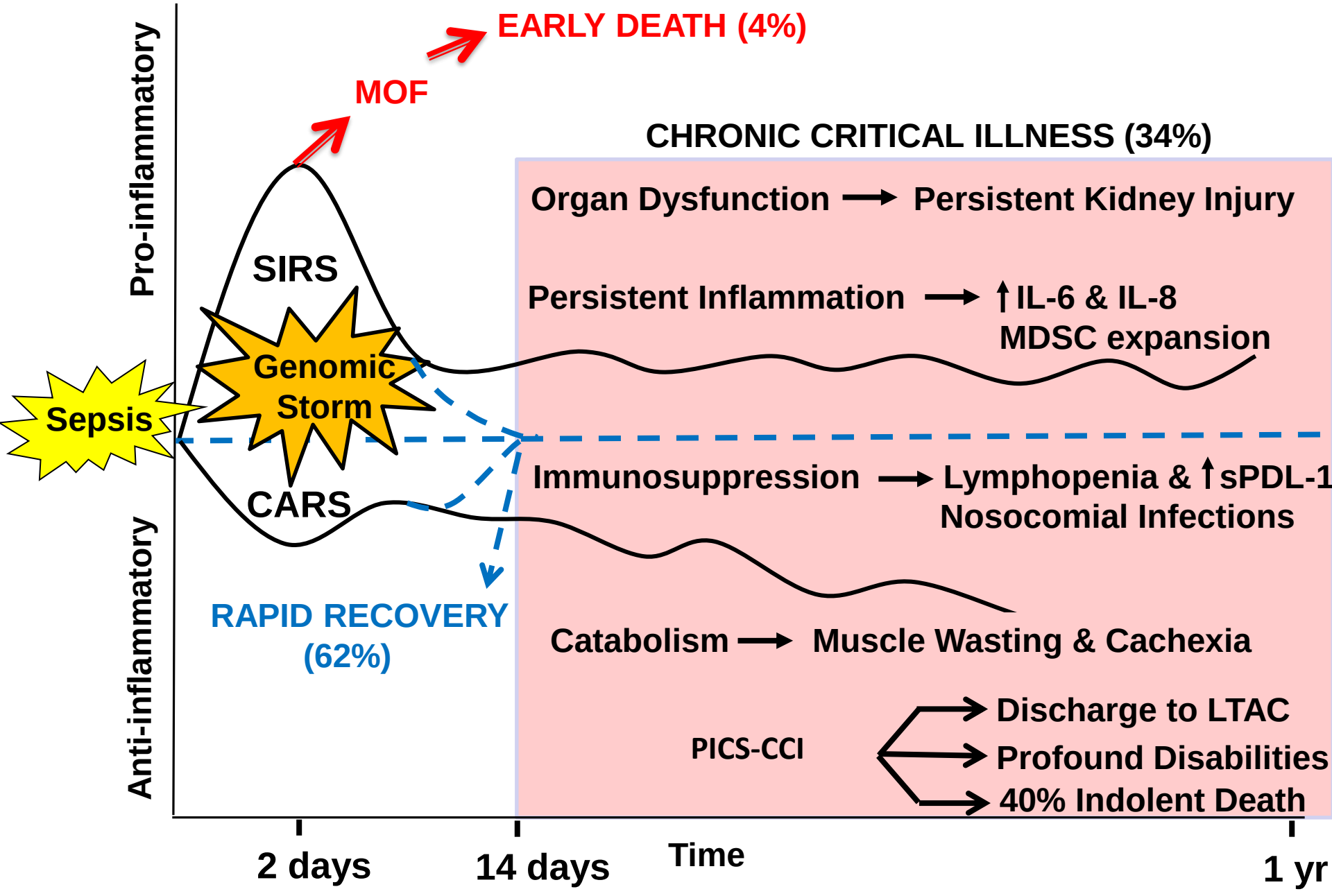
Harmful Effects

Low VEGF/High EPO Ratio:
- Anti-angiogenic State
- Pro-inflammation

Prolong MDSC Expansion:
- Immunosuppression via iNOS, ARG1& IL-10
- Chronic Inflammation via TNF, RANTES & MIP-I
- Lack of Progenitor Stem Cells


NIGMS P50 Team Science Progra
5 Cores & 4 Projects
2014 - 2019
IDR
RedCap
EMR:
EPIC
Core B:
Human
Subjects
Blood
Urine
CTSI:
Biorepository
ICU patients
human research
subject
Core D:
Data
Management
&
Biostatistics
Core C:
Bioanalytics
Core D:
Animal
models
IACUC
IRB
Enrolled 400 patients
Completed 1 year follow-up
Core A:
Administration
Publications
NIGMS reports
Outreach
Web Site & Database
Project 1:
Epidemiology
of CCI & PICS
Institute
of Aging
Clinical data
Biological samples
Analytical results
Reports, publications

Three Clinical Trajectories

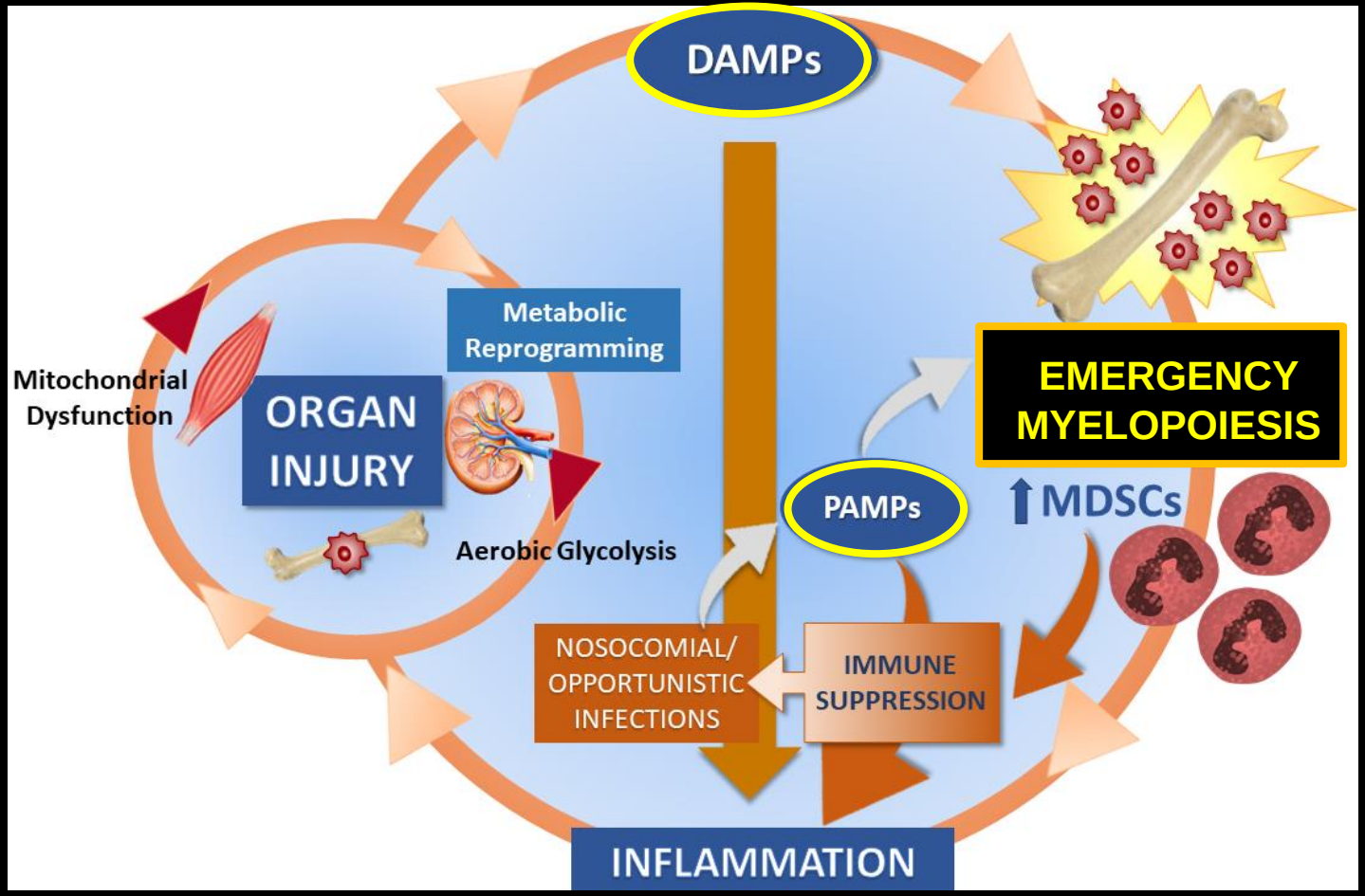


Chronic Critical Illness and the Persistent Inflammation, Immunosuppression, and Catabolism Syndrome.

Russell B. Hawkins, Steven L. Raymond, Julie A. Stortz, Scott Brackenridge, Philip A. Efron, Azra Bihorac, Mark Segal, Frederick A. Moore and ***Lyle L. Moldawer***

Front Immunol 2018

Self Perpetuating Cycle of Inflammation



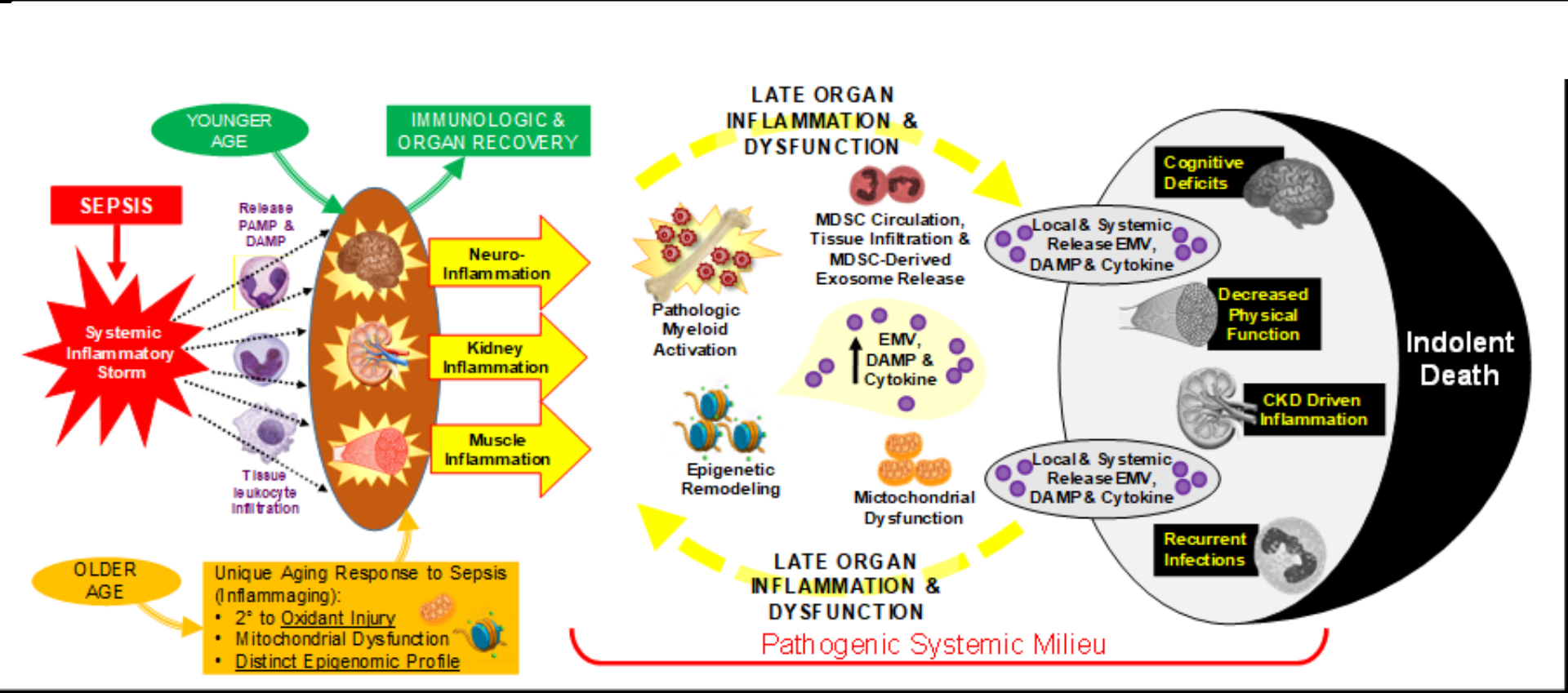
Cartoon

NIGMS RM1 Grant

Phil Efron

Pathophysiology of PICS-CCI in Septic Older Adults

New PO1 Team Science Grant for NIA



Another Cartoon

Summary: Imagination Trumps Knowledge

Pick a Topic and Study Your Patients

Write a Review Article with Collaborators

Construct a Cartoon: Win-Win Testable Hypothesis

Prospectively Test the Hypothesis

Determine Where you were Right and Wrong

Draw Another Cartoon

“ The connection between cause and effect has no beginning and can have no end ”

Leo Tolstoy
War and Peace

“ The connection between cause and effect has no beginning and can have no end “

Leo Tolstoy
War and Peace

“ Imagination is more important than knowledge ”

Albert Einstein