# Translational Systems Biology of Inflammation

## Yoram Vodovotz, Ph.D.

Director, Center for Inflammation and Regenerative Modeling

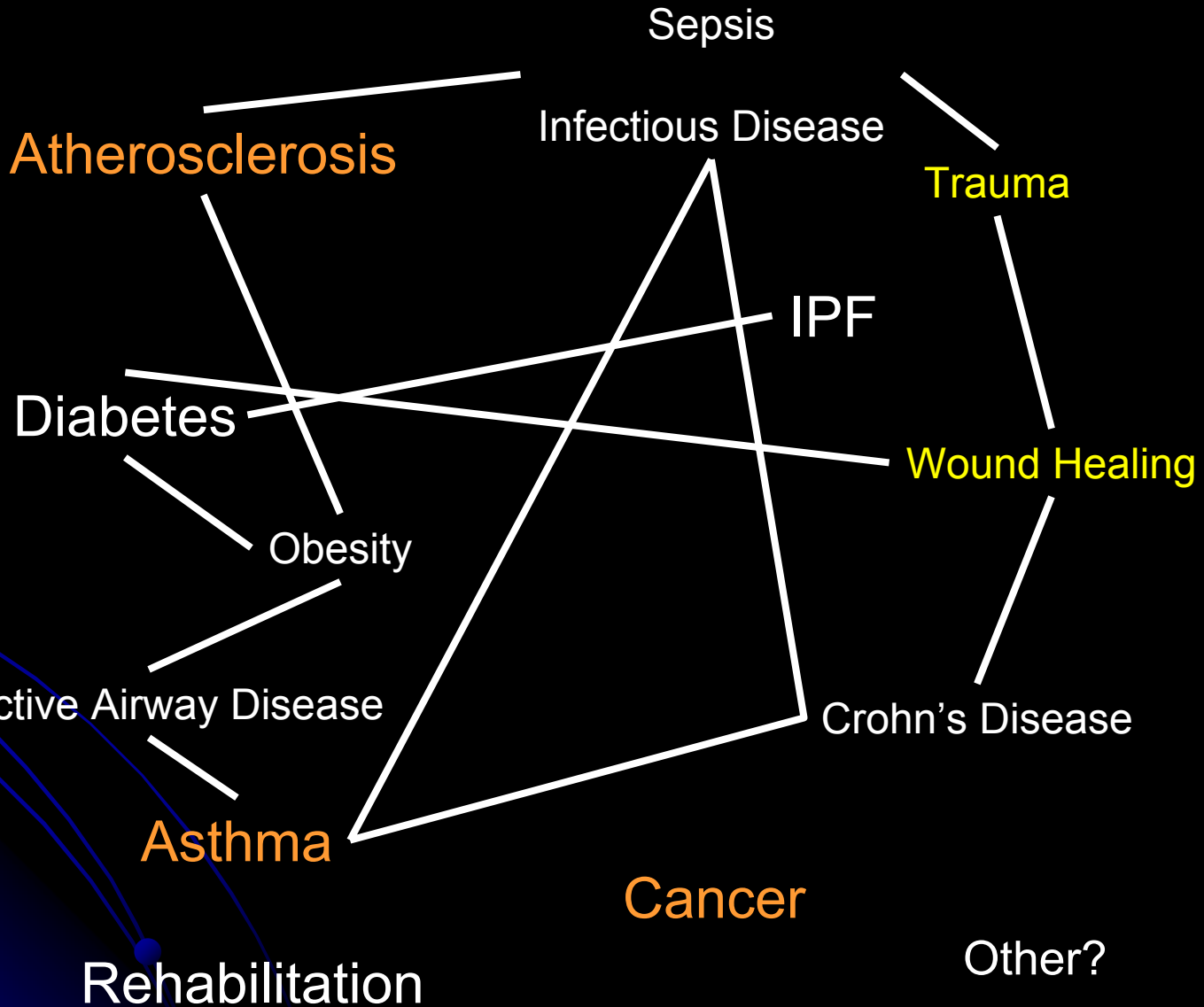Professor of Surgery, Immunology, and Communications Science and Disorder

Visiting Professor of Computational Biology

University of Pittsburgh

*vodovotzy@upmc.edu*

# INFLAMMATION

Sepsis

Infectious Disease

Atherosclerosis

Trauma

IPF

Diabetes

Wound Healing

Obesity

Reactive Airway Disease

Crohn's Disease

Asthma

Cancer

Exercise

Rehabilitation

Other?

# Inflammation is…

- The body's way of informing itself of changes in homeostasis, either from without or within

- Evolutionarily conserved

- Complex, redundant, interconnected

- Necessary for proper healing and regeneration

- Deranged in the settings of trauma, sepsis, chronic diseases, aberrant wound healing

- A puzzle

- **Is Systems Biology the solution?**

From a reductionist approach to inflammation…
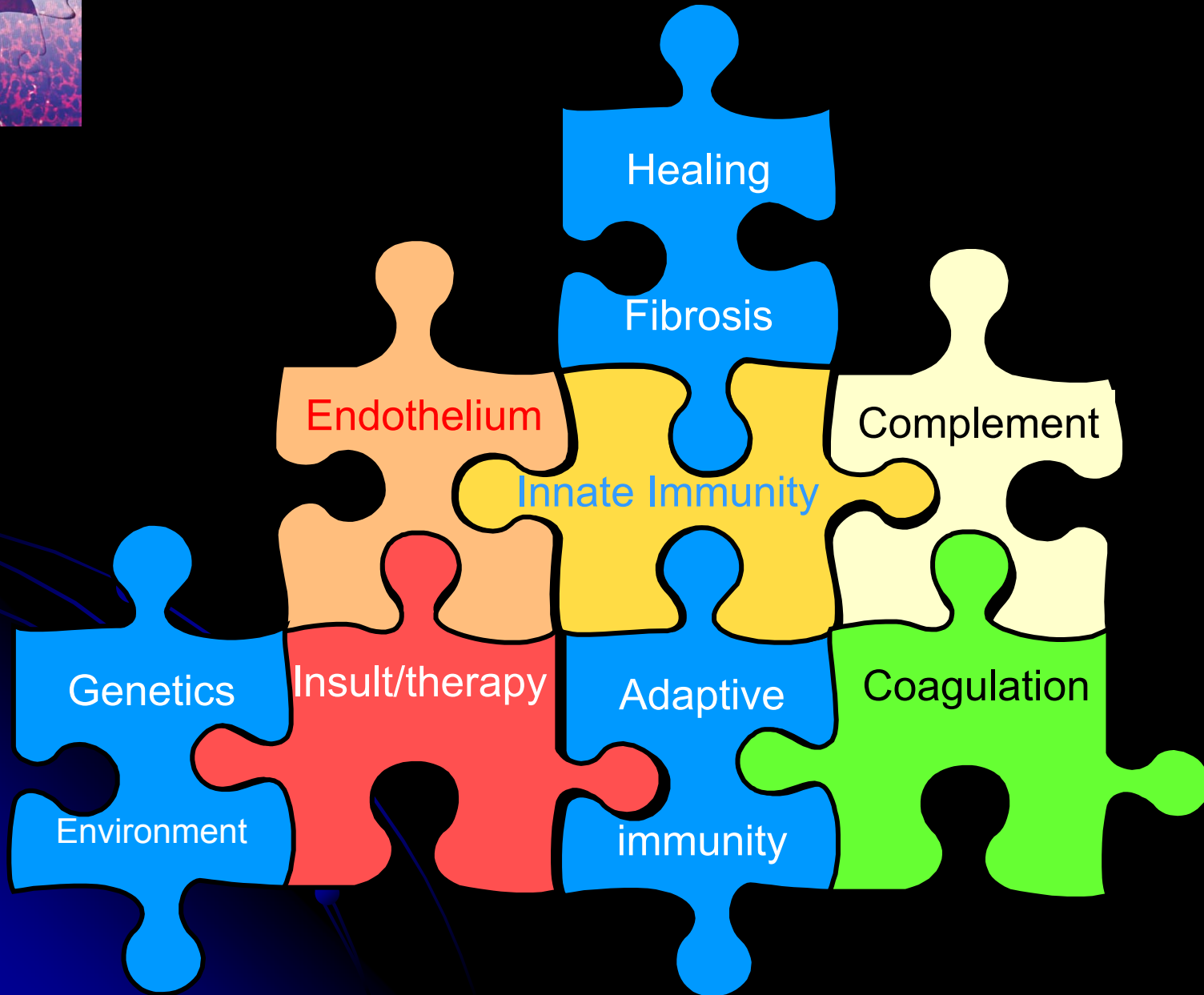
# …to a systems approach using mechanistic computational simulations
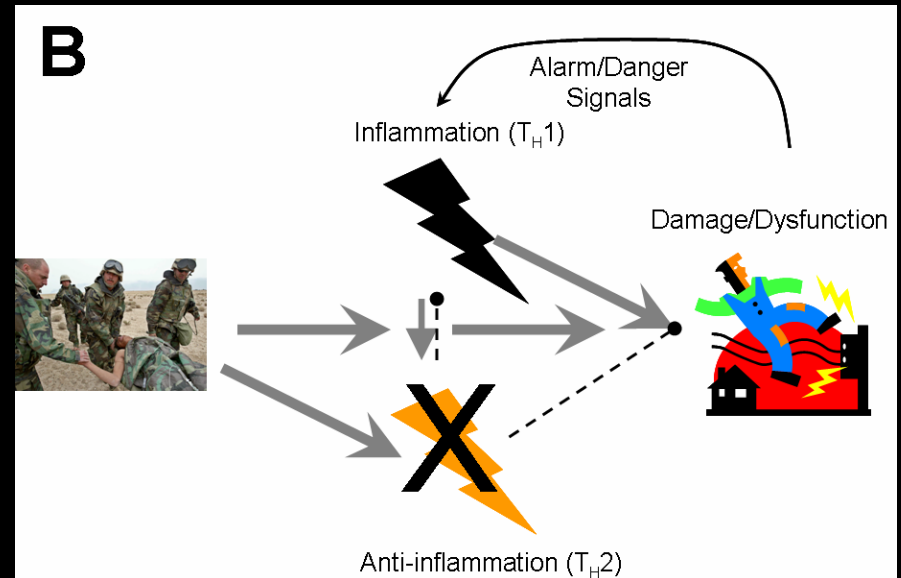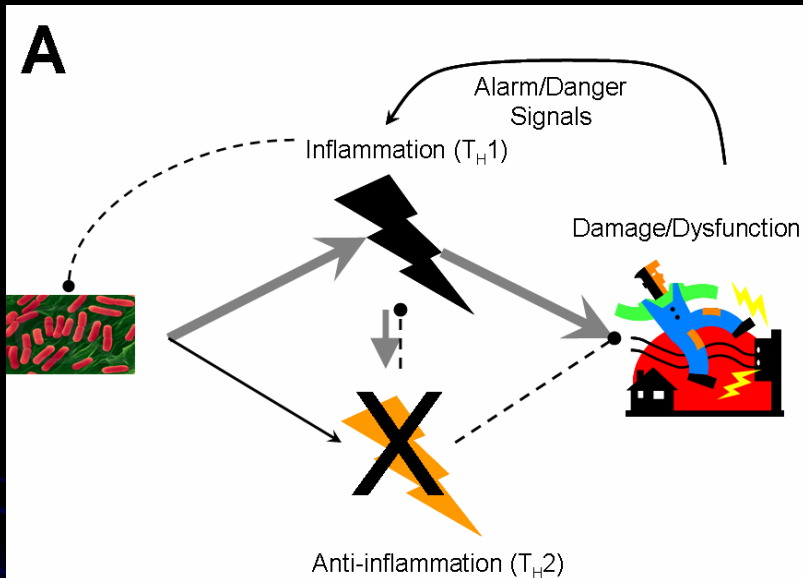


Solid arrow: induction; dashed line: suppression. An initiating stimulus (e.g., pathogen (Panel A) or trauma (Panel B)) stimulates both pro- and anti-inflammatory pathways. In the setting of infection, pro-inflammatory agents (e.g., TNF) cause tissue damage/dysfunction, which in turn stimulates further inflammation (e.g., through the release of "danger signals"). In the case of trauma, tissue damage occurs immediately and further simulates inflammation. Anti-inflammatory agents (e.g., TGF-β1) both suppress inflammation and stimulate healing

(Vodovotz et al, Math Biosci, 2008, In Press).

# The Need for Translational Systems Biology of Inflammation in Shock States
(Vodovotz et al. Mathematical Biosciences. 2008 In Press)

NIH Roadmap / FDA Critical Path

Pre-clinical studies

Clinical trials

In-hospital care

Chronic / rehabilitative care

Inflammation / Healing

Computational Simulations / Genomics

# Translational Systems Biology

An et al. J. Crit. Care. 2007 22:169; An & Vodovotz, J. Burn Care Res. 2008 29:277; Vodovotz et al, PLoS Comput. Biol. 2008 4:1

## "Classical" Systems Biology

Basic insights are primary focus, i.e. "drilling down"

Models structured for greatest basic insights (cellular/molecular interactions, signal transduction)

Simulations designed for laboratory validation

"omics" studies applied to clinically relevant situations, and subsequently subjected to statistical analysis

## Translational Systems Biology

Translational insights are primary focus, i.e. "building up."

Models structured for clinical translational utility (*in silico* clinical trials, diagnostics, rational drug/device design)

Simulations designed for eventual clinical validation

Mechanistic simulations of whole-organism response guide "-omics" studies

# Inflammation Modeling is a Team Sport

- **Critical Care Medicine (Pitt)**
    - **Gilles Clermont**
    - **Mitchell Fink**
    - **John Kellum**
    - **Russ Delude**
    - **Juan Carlos Puyana**
- **Mathematics (Pitt)**
    - **Carson Chow**
    - **Bard Ermentrout**
    - **Jonathan Rubin**
    - **Beatrice Riviere**
    - **Ivan Yotov**
    - **David Swigon**
    - Judy Day
- **Mathematics (CMU)**
    - **Shlomo Ta'asan**
    - Rima Gandlin
- **Statistics (Pitt)**
    - **Greg Constantine**
- **Immunetrics, Inc.**
    - **John Bartels**
    - **Steve Chang**
    - **Arie Baratt**
    - Joydeep Sarkar
- **IBM**
    - **Fred Busche**
- **Northwestern University**
    - **Gary An**
- **University of Cologne**
    - **Eddy Neugebauer**
    - **Rolf Lefering**
- **Ludwig Boltzmann Institute**
    - **Heinz Redl**
- **SUNY-Upstate**
    - **Gary Nieman**
    - **David Carney**
- **Urology (Pitt)**
    - **Michael Chancellor**
    - **Pradeep Tyagi**

- **Surgery (Pitt)**
    - **Tim Billiar**
    - **Ruben Zamora**
    - **Rosie Hoffman**
    - **David Steed**
    - **Juan Ochoa**
    - Claudio Lagoa
    - Andres Torres
    - Rajaie Namas
    - Derek Barclay
    - Mia Jefferson
- **McGowan Institute (Pitt)**
    - **Alan Russell**
    - **John Murphy**
    - **William Federspiel**
    - **William Wagner**
- **SHRS (Pitt)**
    - **Cliff Brubaker**
    - **Kittie Verdolini**
    - **Qi Mi**
    - **Scott Lephart**
    - **David Brienza**
    - **Kelly Fitzgerald**
    - Nicole Li
- **Medicine (Pitt)**
    - **David Whitcomb**
    - **Marc Roberts**
- **Children's Hospital of Pittsburgh**
    - **David Hackam**
    - **Pat Hebda**
    - **Raphael Hirsch**
- **Children's Hospital of Los Angeles**
    - **Jeffrey Upperman**

**All the students of the Systems Approach to Inflammation Course**

# A Systems Approach to Inflammation

## MSCMP3780

A Systems Approach to Inflammation: Course Syllabus
As of September 3, 2007

Wednesdays from 10-12 in 15th Floor BST Conference Room (E1595 BST)

Course Syllabus

Group projects

Registered students

Reference material

Evaluation Forms

SCAI

International Conference for Complexity in Acute Illness

| Date | Topic | Tentative lecturer |
|---|---|---|
| 8/29/07 | A Systems Approach to Inflammation: Basic and Applied Concepts | Y. Vodovotz (Surgery) |
| 9/5/06 | An Introduction to Modeling Complex Biological Systems | G. Clermont (Critical Care Medicine) |
| 9/12/07 | Agent-based Modeling Of Inflammation: Concepts and Practicum | G. An (Northwestern University) (Surgery) |
| 9/19/07 | Facilitating Interdisciplinary Research Using Electronic Tools | Al Cecchetti (Center for Clinical Pharmacology) |
| 9/26/07 | Group Discussion/Modeling Practicum | Vodovotz/Clermont |
| 10/04/07 | Modeling Biological Processes With Differential Equations: Concepts and practicum | Jonathan Rubin(Mathematics) |
| 10/10/07 | Bacteria and the Basic Inflammatory Mechanism | J Fan (Department of Surgery) |
| 10/17/07 | Clinical Trials in Sepsis: Challenges and Translational Role of Modeling | Michael Pinsky (Critical Care Medicine) and Gilles Clermont |
| 10/24/07 | Calibration of complex mathematical models | J. Bartels (Immunetrics, Inc.) and Greg Constantine (Mathematics) |
| 10/31/07 | Modeling the Dynamics and Control of Infection | John Hotchkiss (Critical Care Medicine) |
| 11/7/06 | Modeling the Physiologic Function of Organs | Sven Zenker (Critical Care Medicine) |
| 11/14/06 | Modeling Chronic Inflammation and Adaptive Immunity | Penny Morel (Immunology) |
| 11/21/06 | Thanksgiving Recess (no class) | |
| 11/28/06 | Logical Network Modeling of Biological Processes | S. Ta'asan (Carnegie Mellon University) |
| 12/6/06 | Group Presentations of Final | Students |

http://www.pitt.edu/~cler/mscmp3780/mscmp3780.htm

# Ongoing Modeling Studies at the CIRM

- Trauma / Sepsis
- Skin / vocal fold wound healing
- Necrotizing enterocolitis
- Inflammation-associated carcinogenesis
- The role of inflammation in established cancers
- Vascular injury / atherosclerosis / restenosis
- Urinary tract infections
- Chronic lung diseases (asthma, COPD…)
- Post-spinal cord injury ulcers
- Traumatic brain injury
- Cross-species interactions in malaria
- Integrating modeling with genomics
- The cellular inflammatory response from mRNA to protein

# Cross-cutting Themes

- Translational / commercial applications
  - *In silico* clinical trials
  - Personalized medicine (patient-specific models)
  - Inflammation control strategies
- Basic biology of inflammation
  - *In vitro*
  - *In vivo*
- Software development

# Resources

- Full molecular / cellular / *in vivo* biology lab space

- Computational resources: IBM Shared University Research Award ($500k)

- Two assistant professors, one research instructor

- Technicians and postdocs

# Funding and Resources

- National Institutes of Health

- National Institute on Disability Rehabilitation Research

- Commonwealth of Pennsylvania

- IBM

- Department of Defense

- Pittsburgh Lifesciences Greenhouse