



NSF RTG Retreat

# Translational Systems Biology of Inflammation

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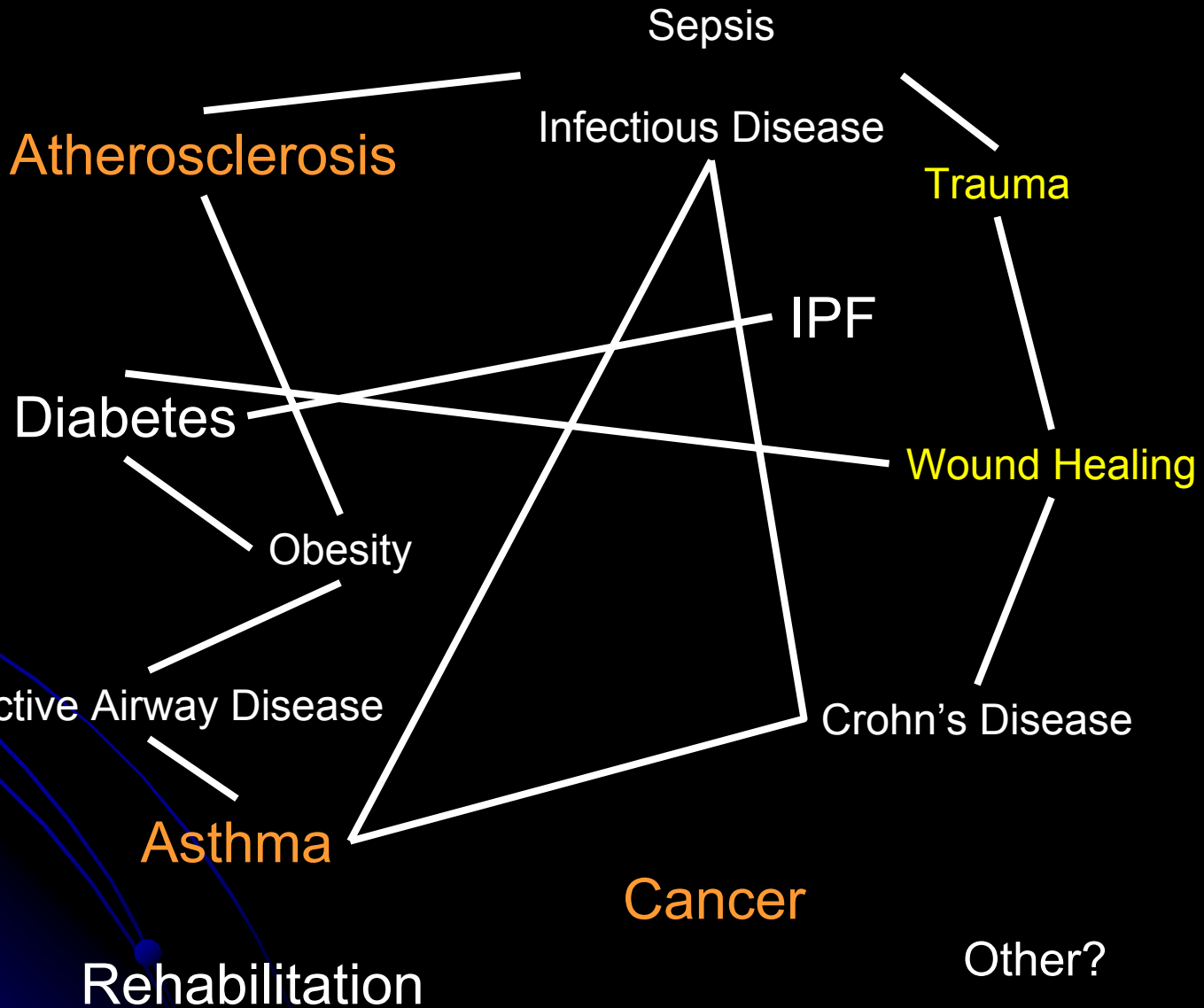
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# INFLAMMATION

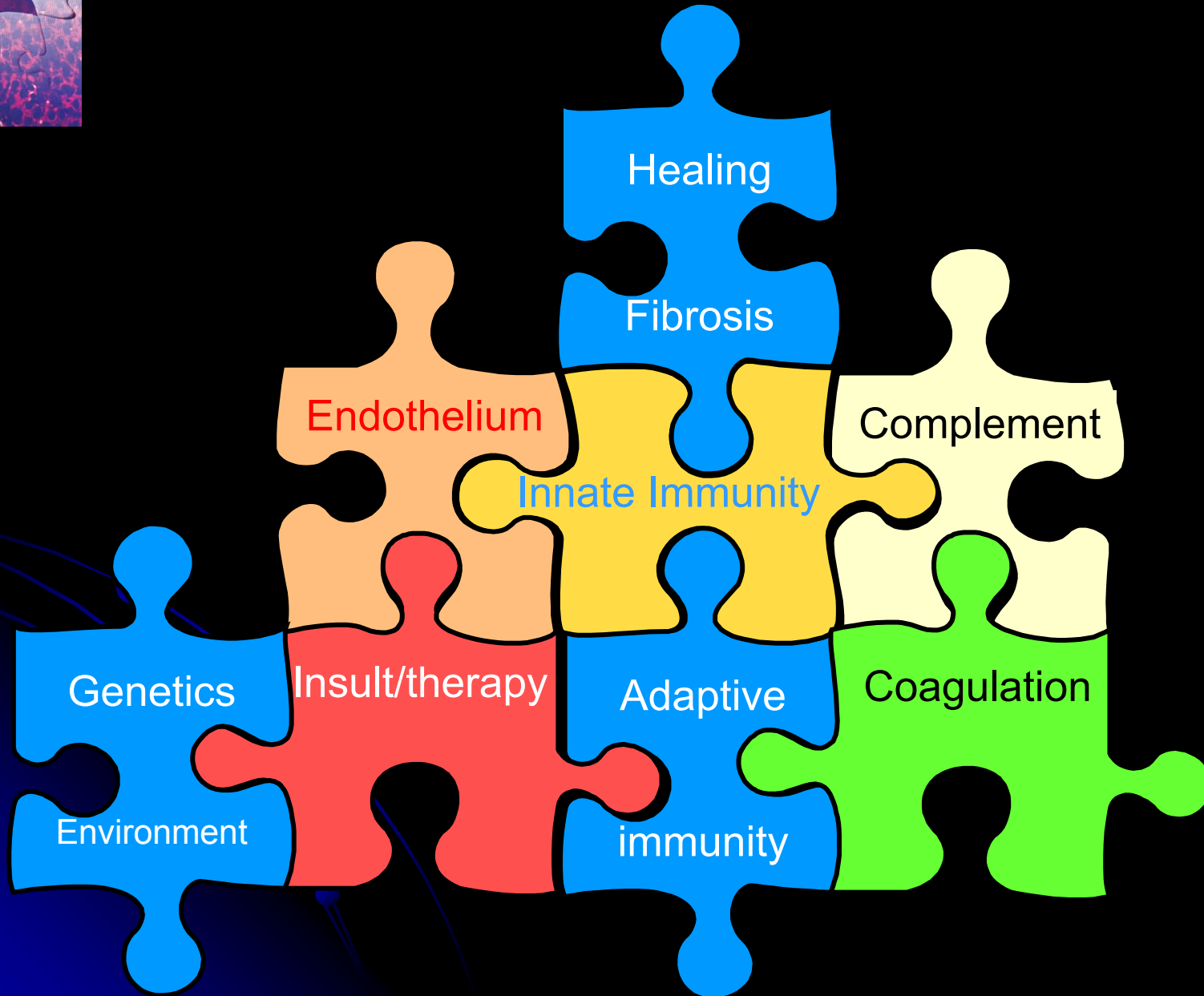




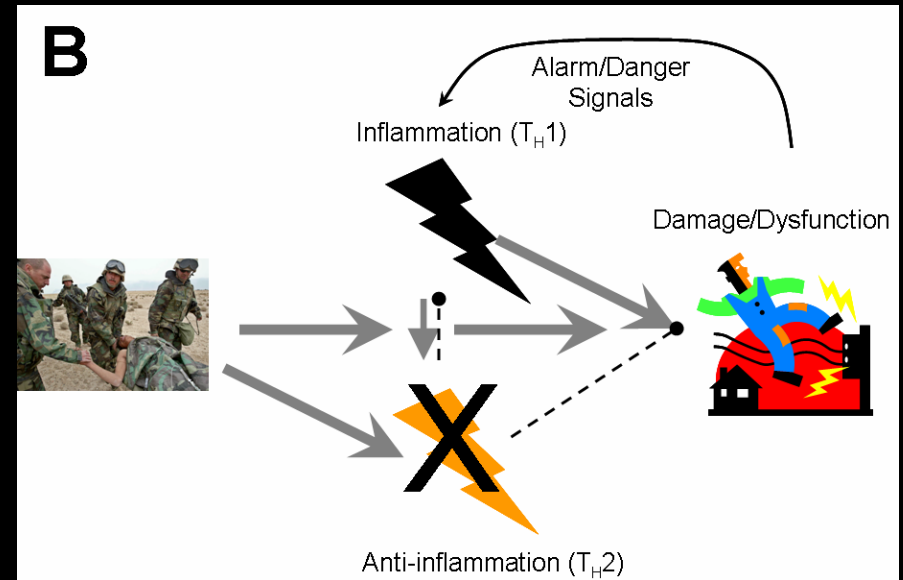
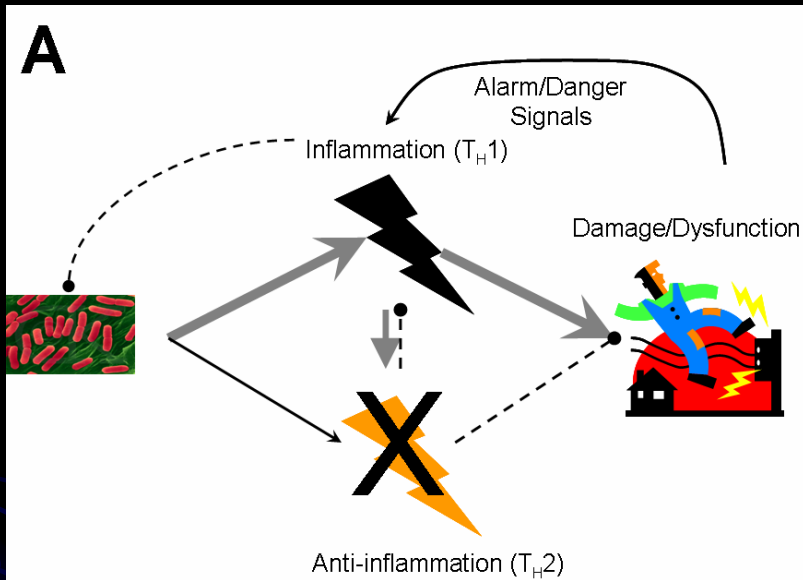
# Inflammation is...

- 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 stimulates inflammation. Anti-inflammatory agents (e.g., TGF- $\beta$ 1) 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

[Course Syllabus](#)

[Group projects](#)

Registered students

[Reference material](#)

[Evaluation Forms](#)

[SCAI](#)

[International Conference for Complexity in Acute Illness](#)

## 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)

Date	Topic	Tentative lecturer
8/29/07	A Systems Approach to Inflammation: Basic and Applied Concepts	<a href="#">Y. Vodovotz (Surgery)</a>
9/5/06	An Introduction to Modeling Complex Biological Systems	<a href="#">G. Clermont (Critical Care Medicine)</a>
9/12/07	Agent-based Modeling Of Inflammation: Concepts and Practicum	<a href="#">G. An (Northwestern University) (Surgery)</a>
9/19/07	Facilitating Interdisciplinary Research Using Electronic Tools	<a href="#">Al Cecchetti (Center for Clinical Pharmacology)</a>
9/26/07	Group Discussion/Modeling Practicum	Vodovotz/Clermont
10/04/07	Modeling Biological Processes With Differential Equations: Concepts and practicum	<a href="#">Jonathan Rubin(Mathematics)</a>
10/10/07	Bacteria and the Basic Inflammatory Mechanism	<a href="#">J Fan (Department of Surgery)</a>
10/17/07	Clinical Trials in Sepsis: Challenges and Translational Role of Modeling	<a href="#">Michael Pinsky (Critical Care Medicine) and Gilles Clermont</a>
10/24/07	Calibration of complex mathematical models	<a href="#">J. Bartels (Immunetrics, Inc.)</a> 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	<a href="#">S. Ta'asan (Carnegie Mellon University)</a>
12/6/06	Group Presentations of Final	Students



# 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