Translational Systems Biology of Inflammation

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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...

- Innate Immunity
- Complement
- Coagulation
- Adaptive Immunity
- Endothelium
- Fibrosis
- Healing
- Insult/therapy
- Genetics
- Environment
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

The Need for Translational Systems Biology of Inflammation in Shock States

NIH Roadmap / FDA Critical Path

Pre-clinical studies | Clinical trials | In-hospital care | Chronic / rehabilitative care

Inflammation / Healing

Computational Simulations / Genomics
Translational Systems Biology

**“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
- Immunetics, 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)

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<th>Date</th>
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<th>Tentative lecturer</th>
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<td>8/29/07</td>
<td>A Systems Approach to Inflammation: Basic and Applied Concepts</td>
<td>Y. Vodovoz (Surgery)</td>
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<tr>
<td>9/5/06</td>
<td>An Introduction to Modeling Complex Biological Systems</td>
<td>G. Clermont (Critical Care Medicine)</td>
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<td>9/12/07</td>
<td>Agent-based Modeling Of Inflammation: Concepts and Practicum</td>
<td>G. An (Northwestern University) (Surgery)</td>
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<td>9/19/07</td>
<td>Facilitating Interdisciplinary Research Using Electronic Tools</td>
<td>A. Cecchetti (Center for Clinical Pharmacology)</td>
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<td>Group Discussion/Modeling Practicum</td>
<td>Vodovoz/Clermont</td>
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<td>10/10/07</td>
<td>Bacteria and the Basic Inflammatory Mechanism</td>
<td>I. Fan (Department of Surgery)</td>
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<td>10/17/07</td>
<td>Clinical Trials in Sepsis: Challenges and Translational Role of Modeling</td>
<td>Michael Pinse (Critical Care Medicine) and Gilles Clermont</td>
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<td>10/24/07</td>
<td>Calibration of complex mathematical models</td>
<td>I. Bartels (Immunetics, Inc.) and Greg Constantin (Mathematics)</td>
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<td>10/31/07</td>
<td>Modeling the Dynamics and Control of Infection</td>
<td>John Hotchkiss (Critical Care Medicine)</td>
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<td>11/7/06</td>
<td>Modeling the Physiologic Function of Organs</td>
<td>Sven Zentler (Critical Care Medicine)</td>
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<td>11/14/06</td>
<td>Modeling Chronic Inflammation and Adaptive Immunity</td>
<td>Penny Morel (Immunology)</td>
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<td>11/21/06</td>
<td>Thanksgiving Recess (no class)</td>
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<td>11/28/06</td>
<td>Logical Network Modeling of Biological Processes</td>
<td>S. Tananu (Carnegie Mellon University)</td>
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<td>12/6/06</td>
<td>Group Presentations of Final</td>
<td>Students</td>
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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