www.mirm.pitt.edu/cirm

The Center for Inflammation and Regenerative Modeling

A Service Model

Yoram Vodovotz, Director
(Department of Surgery, University of Pittsburgh)

Gilles Clermont, Medical Director
(Department of Critical Care Medicine, University of Pittsburgh

International Conference for Systems Biology

Yokohama, October 2006

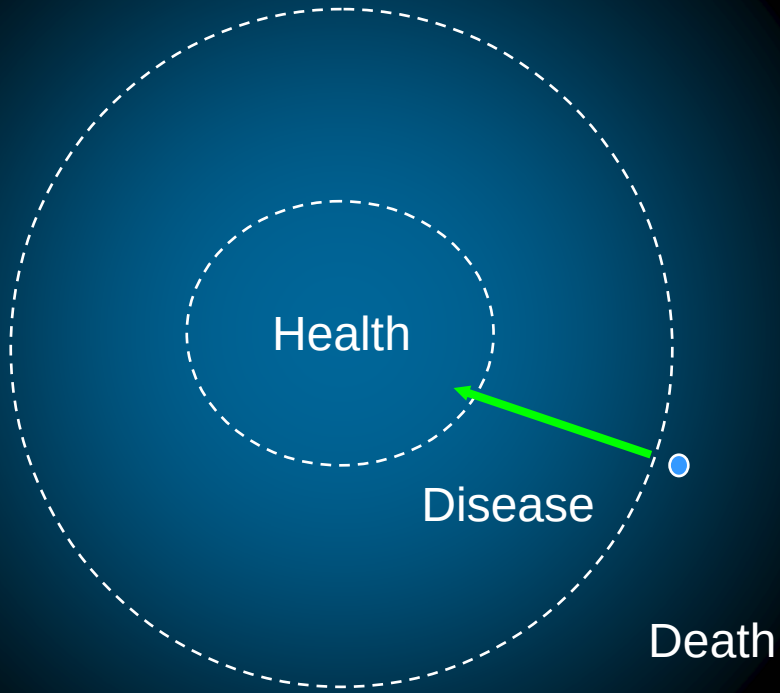
The Era of Interdisciplinary, Translational Research

- The NIH Roadmap Initiative stresses the need to translate the wealth of reductionist data into viable clinical practice through interdisciplinary research
- The FDA “Critical Path” document stresses the need to incorporate computational methods into drug and device design
- Nowhere is this need greater than in the field of inflammation

What is Critical Care?

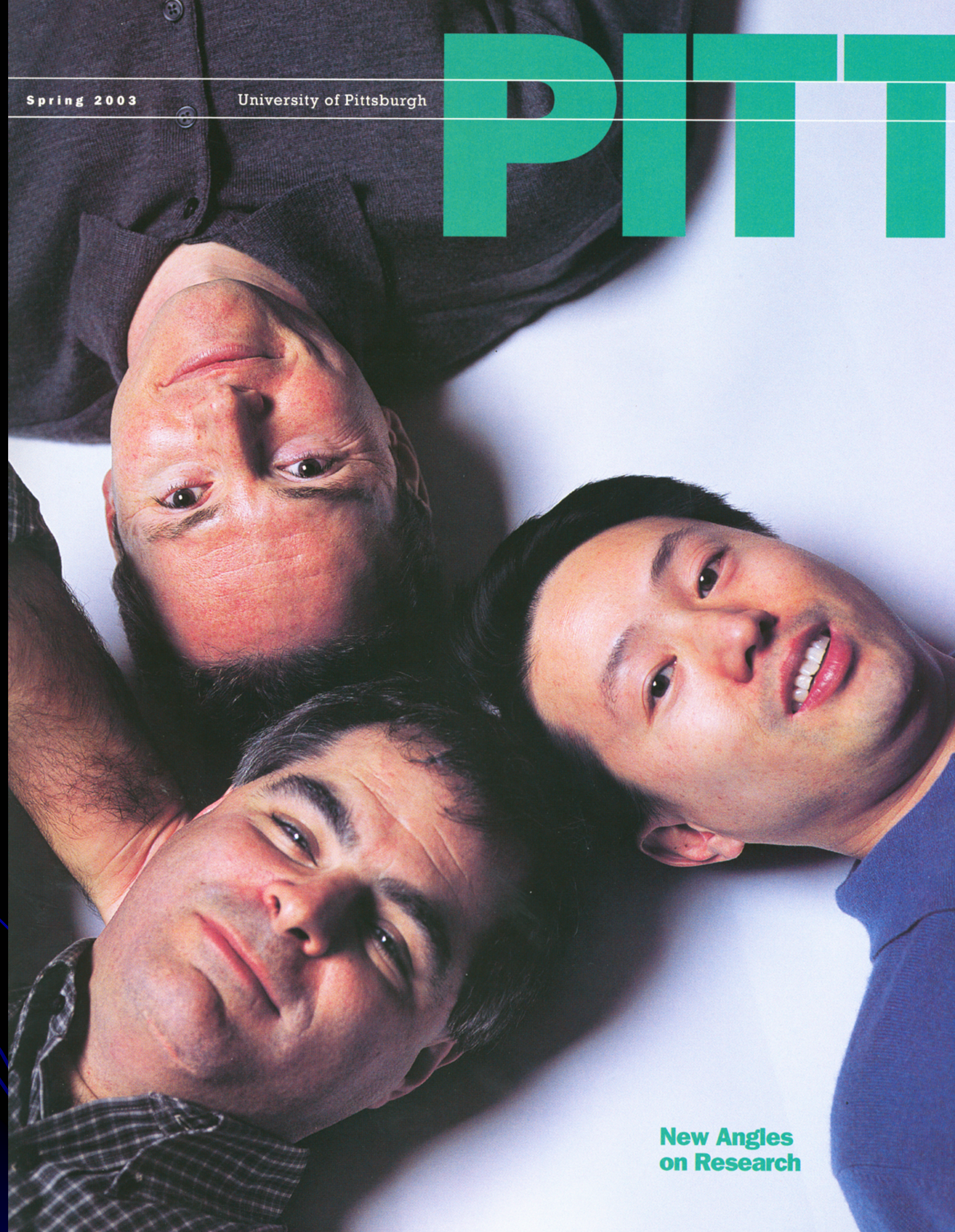
- High mortality and morbidity
- Severe infections (sepsis)
  - >750K cases a year
  - Leading cause of ICU mortality
    - Multiple organ failure
  - **Phase III trials (>200 over 25 years), a dismal record**
- Shock (Trauma, major surgery)
  - 20% will evolve to late organ failure
- Transplantation

Where is Critical Care ?



The CIRM Mission (2005)

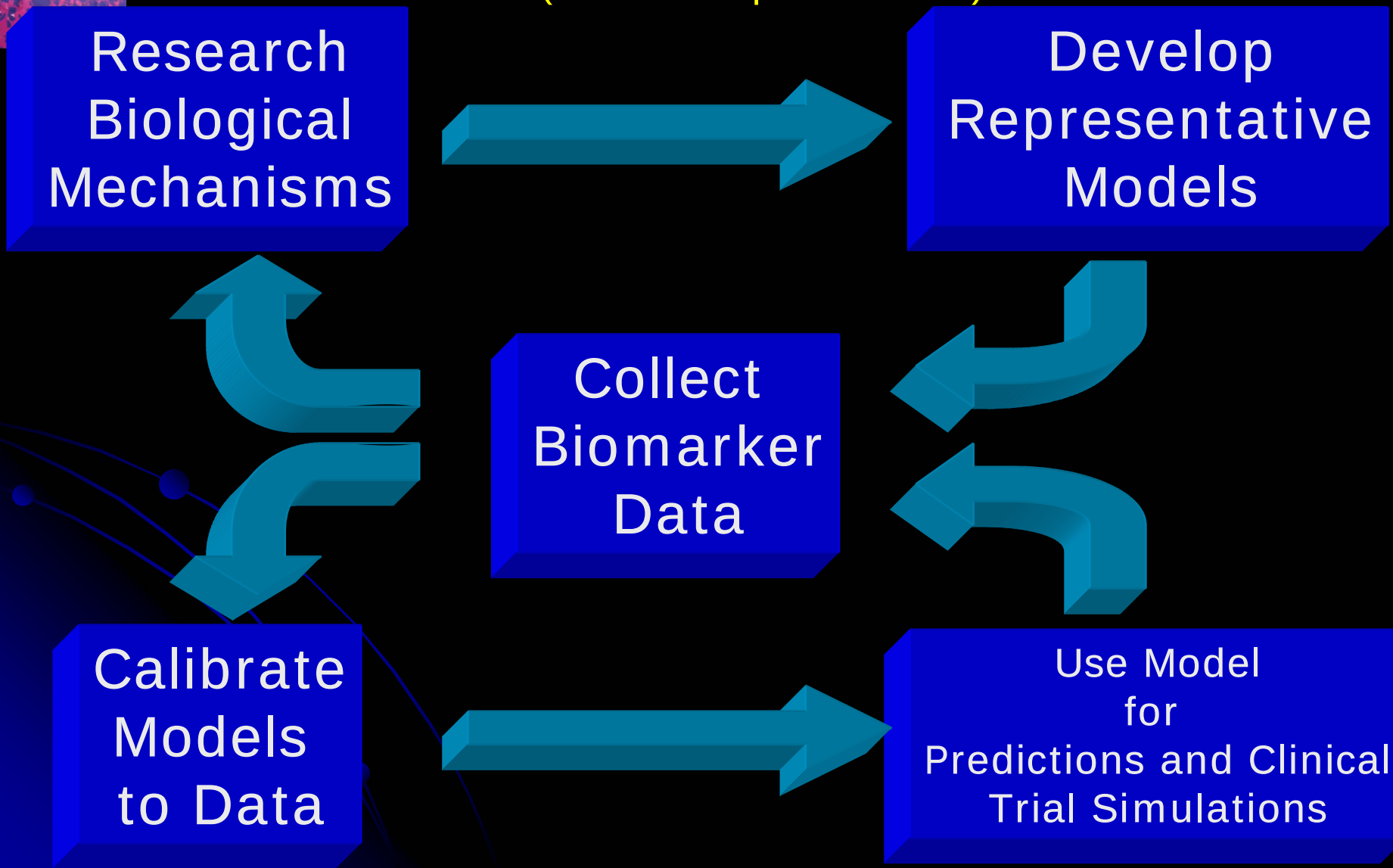
- To bring to bear on the problem of acute and chronic inflammation the interdisciplinary input and enthusiasm of clinicians, bench scientists, and modelers, from both research institutions and companies
- To facilitate the design of regenerative medicine approaches by understanding the underlying inflammatory processes and the inflammatory impact of therapies
- To harness the intrinsic regenerative power of the human body by modeling not only specific organs but also the inflammatory communication network that binds them together


Spring 2003
University of Pittsburgh
PITT
New Angles
on Research

Inflammation Modeling is a Team Sport

- Mathematics (Pitt)
  - **Carson Chow**
  - **Bard Ermentrout**
  - **Jonathan Rubin**
  - **Beatrice Riviere**
  - **Ivan Yotov**
  - **David Swigon**
  - Judy Day
  - Qi Mi
- Mathematics (CMU)
  - **Shlomo Ta'asan**
  - Rima Gandlin
- Statistics (Pitt)
  - **Greg Constantine**
- Immunetrics, Inc.
  - **John Bartels**
  - **Steve Chang**
  - **Arie Baratt**
  - Joyce Wei
- IBM
  - **Fred Busche**
- Cook County Hospital
  - **Gary An**
- University of Cologne
  - **Eddy Neugebauer**
  - **Rolf Lefering**
- Ludwig Boltzmann Institute
  - **Heinz Redl**
- SUNY-Upstate
  - **Gary Nieman**
  - **David Carney**
- Surgery (Pitt)
  - **Tim Billiar**
  - **Ruben Zamora**
  - **Rosie Hoffman**
  - **David Hackam**
  - **Robert Kormos**
  - **David Steed**
  - **Edith Tzeng**
  - **Juan Ochoa**
  - Claudio Lagoa
  - Andres Torres
  - Binnie Bitten
  - Derek Barclay
  - Thierry Clermont
- Critical Care Medicine (Pitt)
  - **Gilles Clermont**
  - **Mitchell Fink**
  - **John Kellum**
  - **Russ Delude**
  - **Juan Carlos Puyana**
- McGowan Institute (Pitt)
  - **Alan Russell**
  - **John Murphy**
  - **William Federspiel**
  - **William Wagner**
- SHRS (Pitt)
  - **Cliff Brubaker**
  - **Kittie Verdolini**
- Medicine (Pitt)
  - **David Whitcomb**
  - **Marc Roberts**
- Children's Hospital of Pittsburgh
  - **David Hackam**
  - **Jeffrey Upperman**
  - **Pat Hebda**
  - **Raphael Hirsch**

Simulating inflammation at the Center for Inflammation and Regenerative Modeling, McGowan Institute for Regenerative Medicine
(www.mirm.pitt.edu/cirm)



Modeling Inflammation at the CIRM

- Have developed multiple models of acute inflammation (sepsis, trauma/hemorrhage, biowarfare agents, phonotrauma, wound healing), organ damage/dysfunction, and healing/regeneration
  - Qualitative and quantitative predictions
  - Probing mechanisms
- Have simulated device usage and guided device design
- Have outlined an iterative strategy for rational drug design and administration
- Have carried out simulated clinical trials in the settings of sepsis and trauma, including biowarfare applications

Reduced models of inflammation

A reduced mathematical model of the acute inflammatory response: I. Derivation of model and analysis of anti-inflammation

Angela Reynolds[a], Jonathan Rubin[a,*], Gilles Clermont[b,c,d], Judy Day[a], Yoram Vodovotz[b,c,e], G. Bard Ermentrout[a]

[a]*Department of Mathematics, 301 Thackeray, University of Pittsburgh, Pittsburgh, PA 15260, USA*
[b]*CIRM (Center for Inflammation and Regenerative Modeling), 100 Technology Drive Suite 200, Pittsburgh, PA 15219-3110, USA*
[c]*CRISMA Laboratory, University of Pittsburgh, Pittsburgh, PA 15261, USA*
[d]*Department of Critical Care Medicine, 3550 Terrace St., University of Pittsburgh Medical Center, Pittsburgh, PA 15261, USA*
[e]*Department of Surgery, University of Pittsburgh Medical Center, W1542 Biomedical Sciences Tower, 200 Lothrop St., Pittsburgh, PA 15213, USA*

A reduced mathematical model of the acute inflammatory response II. Capturing scenarios of repeated endotoxin administration

Judy Day[a], Jonathan Rubin[a,*], Yoram Vodovotz[b,c,d], Carson C. Chow[e], Angela Reynolds[a], Gilles Clermont[f,c,d]

[a]*Department of Mathematics, 301 Thackeray, University of Pittsburgh, Pittsburgh, PA 15260, USA*
[b]*Department of Surgery, University of Pittsburgh Medical Center, W1542 Biomedical Sciences Tower, 200 Lothrop St., Pittsburgh, PA 15213, USA*
[c]*Center for Inflammatory and Regenerative Medicine (CIRM), 100 Technology Drive Suite 200, Pittsburgh, PA 15219-3110, USA*
[d]*CRISMA Laboratory, University of Pittsburgh, Pittsburgh, PA 15261, USA*
[e]*Laboratory of Biological Modeling, NIDDK, NIH, Bethesda, MD 20892, USA*
[f]*Department of Critical Care Medicine, 3550 Terrace St, University of Pittsburgh Medical Center, Pittsburgh, PA 15261, USA*

A Unified Inflammatory Response

THE ACUTE INFLAMMATORY RESPONSE IN DIVERSE SHOCK STATES

Carson C. Chow,* Gilles Clermont,† Rukmini Kumar,‡ Claudio Lagoa,§ Zacharia Tawadrous,† David Gallo,§ Binnie Betten,§ John Bartels,‖ Gregory Constantine,* Mitchell P. Fink,† Timothy R. Billiar,§ and Yoram Vodovotz§

*Department of Mathematics, †Department of Critical Care Medicine, ‡Department of Physics and Astronomy, and §Department of Surgery, University of Pittsburgh, Pittsburgh, Pensylvania; and ‖Immunetrics, Inc., Pittsburgh, Pennsylvania

Probing mechanisms

In Silico and In Vivo Approach to Elucidate the Inflammatory Complexity of CD14-deficient Mice

Jose M Prince,[1] Ryan M Levy,[1] John Bartels,[2] Arie Baratt,[2] John M Kane, III,[1] Claudio Lagoa,[1] Jonathan Rubin,[3,5] Judy Day,[3] Joyce Wei,[2] Mitchell P Fink,[1,4,5] Sanna M Goyert,[6] Gilles Clermont,[4,5] Timothy R Billiar,[1,5] and Yoram Vodovotz[1,5,7]

[1]Department of Surgery, University of Pittsburgh, Pittsburgh, PA, USA; [2]Immunetrics, Inc., Pittsburgh, PA, USA; [3]Department of Mathematics, University of Pittsburgh, Pittsburgh, PA, USA; [4]Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA, USA; [5]McGowan Institute for Regenerative Medicine, Center for Inflammation and Regenerative Modeling, University of Pittsburgh, Pittsburgh, PA, USA; [6]North Shore-Long Island Jewish Research Institute/New York University School of Medicine, Manhasset, NY, USA; [7]Department of Immunology, University of Pittsburgh, Pittsburgh, PA, USA

In silico design of RCTs

In silico design of clinical trials: A method coming of age

Gilles Clermont, MD; John Bartels; Rukmini Kumar, MSc; Greg Constantine, PhD; Yoram Vodovotz, PhD; Carson Chow, PhD

Objective: To determine the feasibility and potential usefulness of mathematical models in evaluating immunomodulatory strategies in clinical trials of severe sepsis.

Design: Mathematical modeling of immunomodulation in simulated patients.

Setting: Computer laboratory.

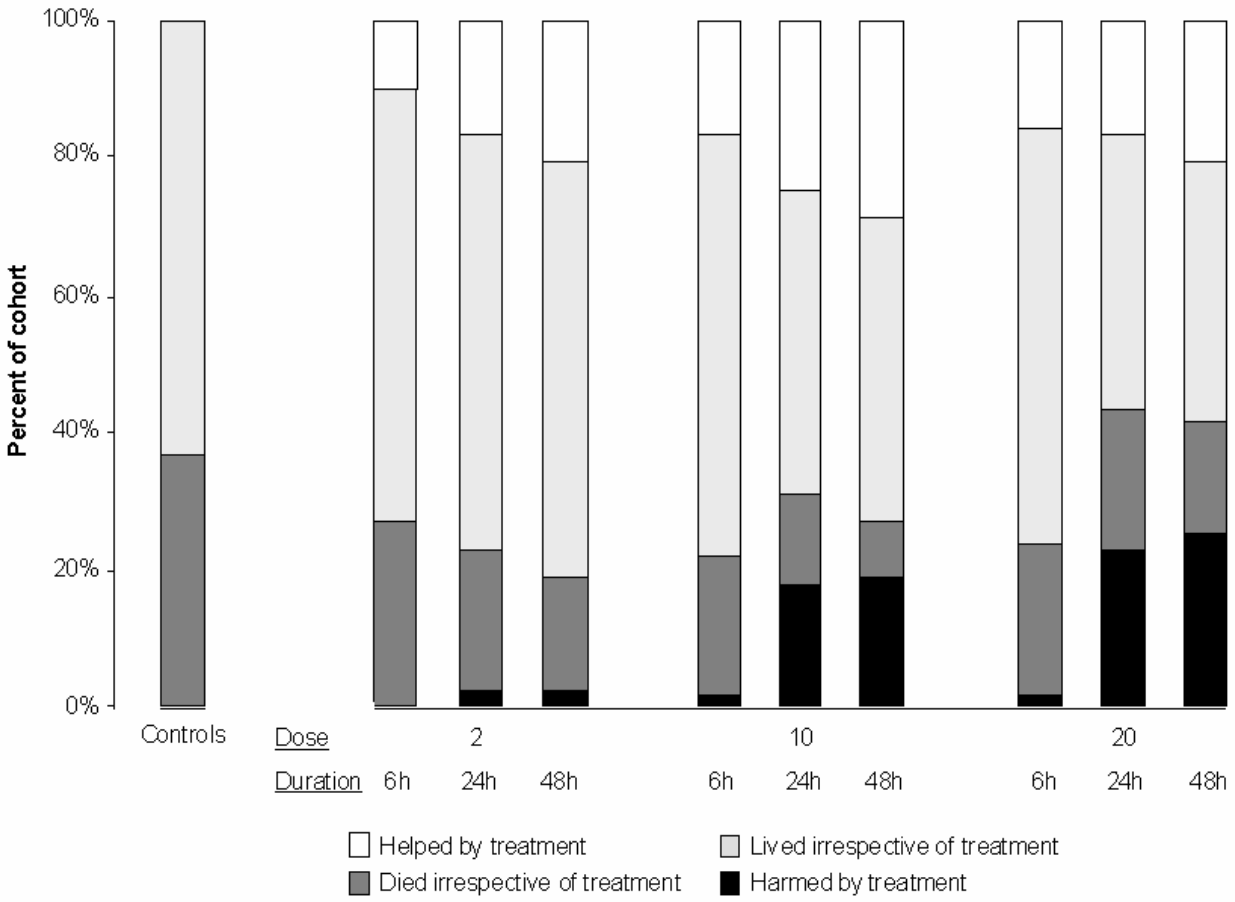
Measurements and Main Results: We introduce and evaluate the concept of conducting a randomized clinical trial *in silico* based on simulated patients generated from a mechanistic mathematical model of bacterial infection, the acute inflammatory response, global tissue dysfunction, and a therapeutic intervention. Trial populations are constructed to reflect heterogeneity in bacterial load and virulence as well as propensity to mount and modulate an inflammatory response. We constructed a cohort of 1,000 trial patients submitted to therapy with one of three different doses of a neutralizing antibody directed against tumor necrosis factor (anti-TNF) for 6, 24, or 48 hrs. We present cytokine profiles over time and expected outcome for each cohort. We identify subgroups with high propensity for being helped or harmed by the proposed intervention and identify early serum markers for each of those subgroups.

The mathematical simulation confirms the inability of simple markers to predict outcome of sepsis. The simulation clearly separates cases with favorable and unfavorable outcome on the basis of global tissue dysfunction. Control survival was 62.9% at 1 wk. Depending on dose and duration of treatment, survival ranged from 57.1% to 80.8%. Higher doses of anti-TNF, although effective, also result in considerable harm to patients. A statistical analysis based on a simulated cohort identified markers of favorable or adverse response to anti-TNF treatment.

Conclusions: A mathematical simulation of anti-TNF therapy identified clear windows of opportunity for this intervention as well as populations that can be harmed by anti-TNF therapy. The construction of an *in silico* clinical trial could provide profound insight into the design of clinical trials of immunomodulatory therapies, ranging from optimal patient selection to individualized dosage and duration of proposed therapeutic interventions. (Crit Care Med 2004; 32:2061–2070)

KEY WORDS: sepsis; immunomodulation; inflammation; computer simulation; clinical trial; anti-tumor necrosis factor

Anti-TNF treatment for sepsis: A simulation study



Clermont et al. 2004

The Service Model

Research group with a specific project

- •Understanding the determinants of hemorrhagic shock
- •Pathogenesis of acute pancreatitis
- •Assessment of disease activity in Juvenile Rhumatoid arthritis

CIRM contact to define where modeling could augment the scientific value of the project

- •Define key personnel and extent of CIRM involvement
- •Define resources and budget
- •Define logistics

CIRM personnel's involvement remains central during execution phase

- •Appropriate data/techniques used
- •Reporting on execution
- •Scientific disseminiation

CIRM-Related Educational Initiatives Graduate Courses

- Systems Approach to Inflammation (CMP 3780)
- Immunology and Human Disease (IGP 3230)
- Vaccines and Immunity (MVMG 3440)
- Cell and Systems Modeling (COMPBIO 2040)
- Modeling Approaches for Biological Processes (BIOINF3115)

CIRM Facilities / Resources

- Physical Space
- Laboratory facilities
  - Animal laboratory
  - High throughput capabilties (Luminex)
- Inflammatory biomarker database
- Funding

Current Funding for CIRM Activities: ~$9M

- Systems Engineering of Pheresis Intervention for Sepsis (PI: Kellum; NHLBI)
- Modeling the Acute Inflammatory Response (PI: Clermont; NIGMS)
- Molecular Biology of Hemorrhagic Shock (PI: Billiar). Project V: Predictive Mathematical Model of Inflammation) (PI: Vodovotz; NIGMS)
- Metabolic-Inflammatory Systems in Irreversible Shock (PI: Puyana; NHLBI)
- Artificial and Biohybrid devices, Therapeutic Applications of Regenerative Medicine and Technologies for Tissue Engineering (Overal PI: Russell). Agent-based Model of Diabetic Foot Ulcers: *In Vitro* and *In Silico* Studies (PI: Vodovotz; Commonwealth of Pennsylvania)
- The International Conference on Complexity in Acute Illness (PI: Clermont; NIGMS)

CIRM Personnel / Hires

- Sven Zenker (CIRM Fellow)
- Sylvia Daun (CIRM Fellow)
- Derek Barclay (Luminex technician)
- Arvinder Chaudhary (Oracle database)

CIRM-Related Scientific Dissemination

- Published manuscripts: 15
- Plenary / invited presentations at several international meetings
- Journal of Critical Care

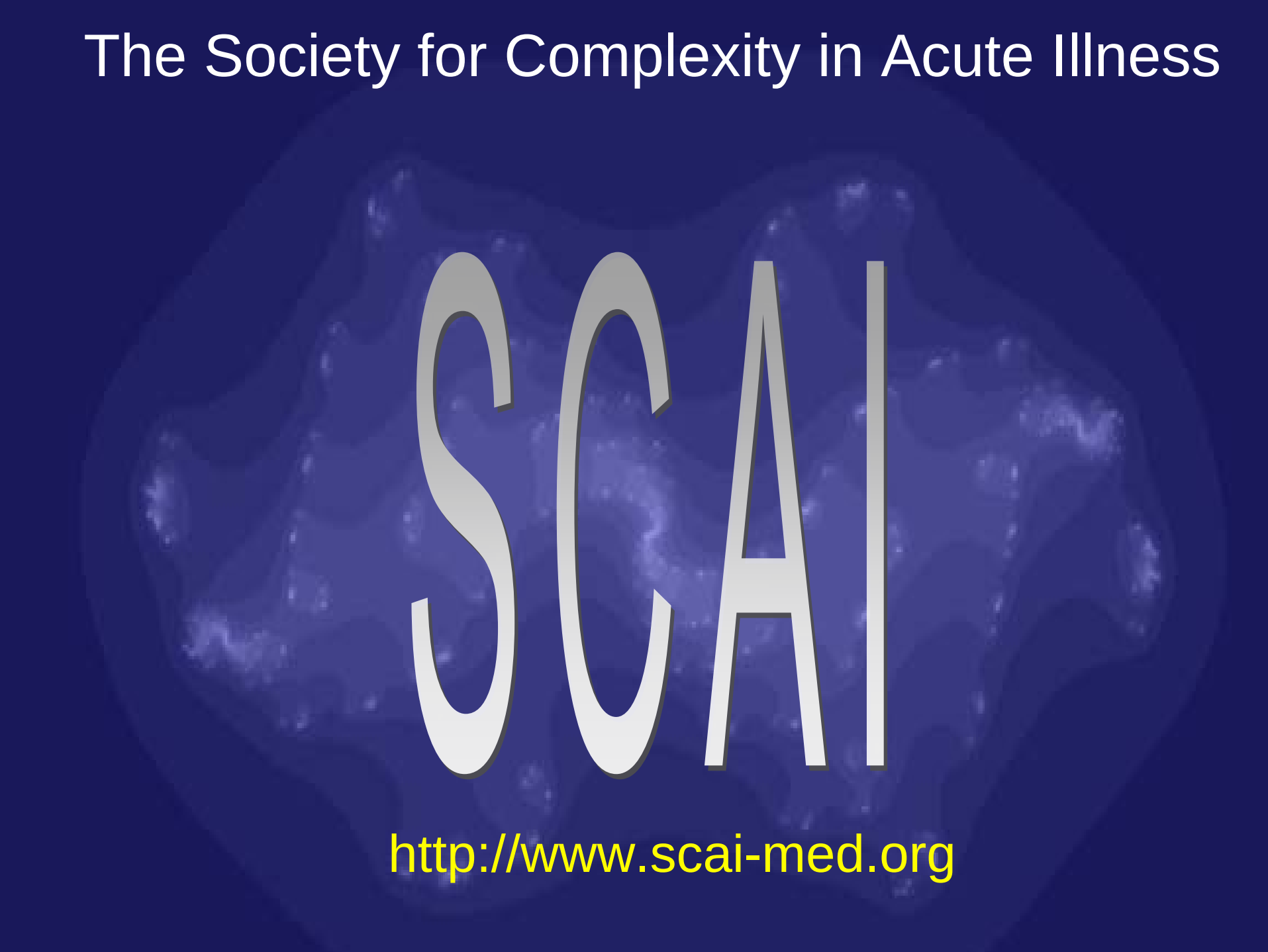
Oversight / Governance

- Executive committee
- Internal (institutional) Advisory Board
  - Yearly
- External Advisory Board
- CIRM retreat
  - Twice a year

Ongoing Issues

- Cohesion maintained by few individuals
- Funding
- Who calls on CIRM
  - Balance between quantitative scientists and clinicians/bioscientists
- Balance of Service vs. Mission
  - Chronic Illness
  - Cancer

The Society for Complexity in Acute Illness



http://www.scai-med.org

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International Conference on Complexity in Acute Illness

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5th International Conference on Complexity in Acute Illness

5th International Conference on Complexity in Acute Illness
October 19, 20, 21, 2006
Ritz-Carlton Hotel
Tyson's Corner, Virginia

www.iccai.org

Critical illness is the result of the interplay of complex physiology, complex decision making and a complex environment. ICCAI 2006 gathers outstanding mathematicians, engineers, biological scientists, clinicians and industry participants to present recent advances in filling the translation gap between advances in quantitative sciences and improved bedside decision making resulting in improved patient outcomes.

Abstract submissions are encouraged and will be published in the December edition of the Journal of Critical Care