

Symposium on Automation and Decision Support Systems  
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# A Self-Adaptive Inflammation Control Device: Insights from Mathematical Modeling of Inflammation

Yoram Vodovotz



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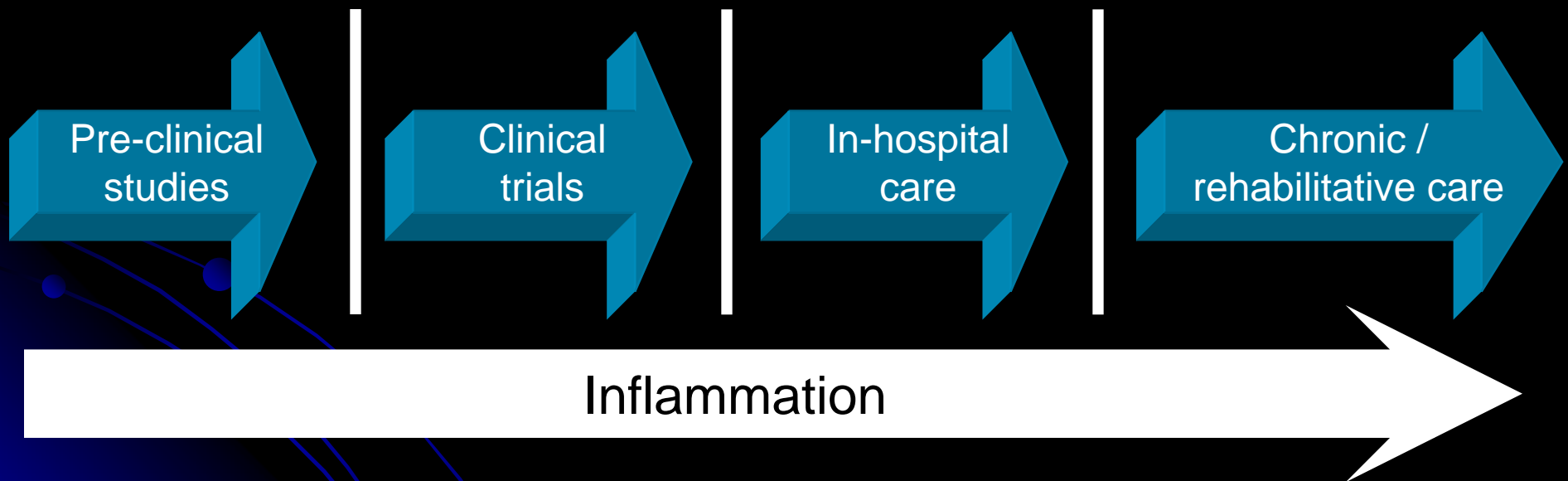
University of Pittsburgh

[www.mirm.pitt.edu/cirm](http://www.mirm.pitt.edu/cirm)

*Disclosure:* Co-founder of and stakeholder in Immunetrics, Inc.



# Traversing the Fragmented Continuum of Healthcare Delivery for Trauma and Sepsis





# Inflammation is...

- The body's way of informing itself of changes in homeostasis, either from without or within
- Evolutionarily conserved
- Complex, redundant, interconnected
  - Cannot determine whole from sum of parts
  - Changes with time, context
  - Positive and negative feedback loops
  - Highly adaptable and resistant to many perturbations
  - Robustness is in part due to the compartmentalization of inflammation in many different dimensions (gene networks, cellular networks, crosstalk among tissues, among organisms, among populations)
  - ...but, highly susceptible to degradation of central control points under certain conditions (i.e., disease)
- Necessary for proper healing and regeneration
- Deranged in the settings of trauma, sepsis, chronic inflammatory diseases
- A puzzle
- **Is Systems Biology the solution?**

## Review

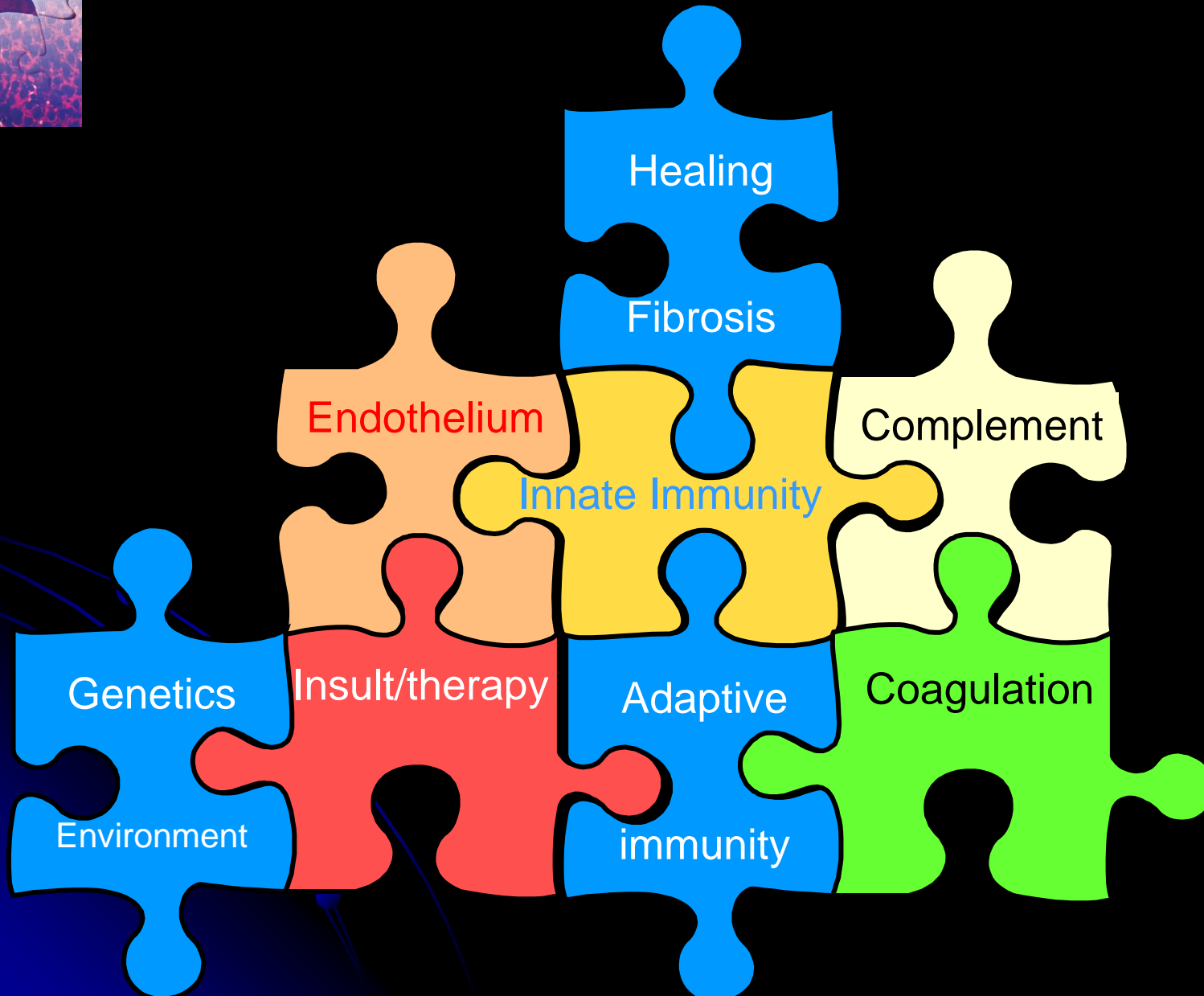
## Translational Systems Biology of Inflammation

Yoram Vodovotz<sup>1,2\*</sup>, Marie Csete<sup>3</sup>, John Bartels<sup>4</sup>, Steven Chang<sup>4</sup>, Gary An<sup>2,5</sup>

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- At the McGowan Institute's Center for Inflammation and Regenerative Modeling, we have developed a series of mathematical models of inflammation and its interactions with tissue damage, with the goal of understanding, predicting, and controlling inflammation.
- Our therapeutic goal is not to abolish inflammation *per se* but to reduce damage or dysfunction (i.e. promote healing) by modulating inflammation in a rational fashion.
- We have concentrated on *in silico* clinical trials, personalized diagnostics, and rational drug / device design, with basic insights being secondary

# From a reductionist approach to inflammation...



... To a Systems Approach to Inflammation: **The response to infection**

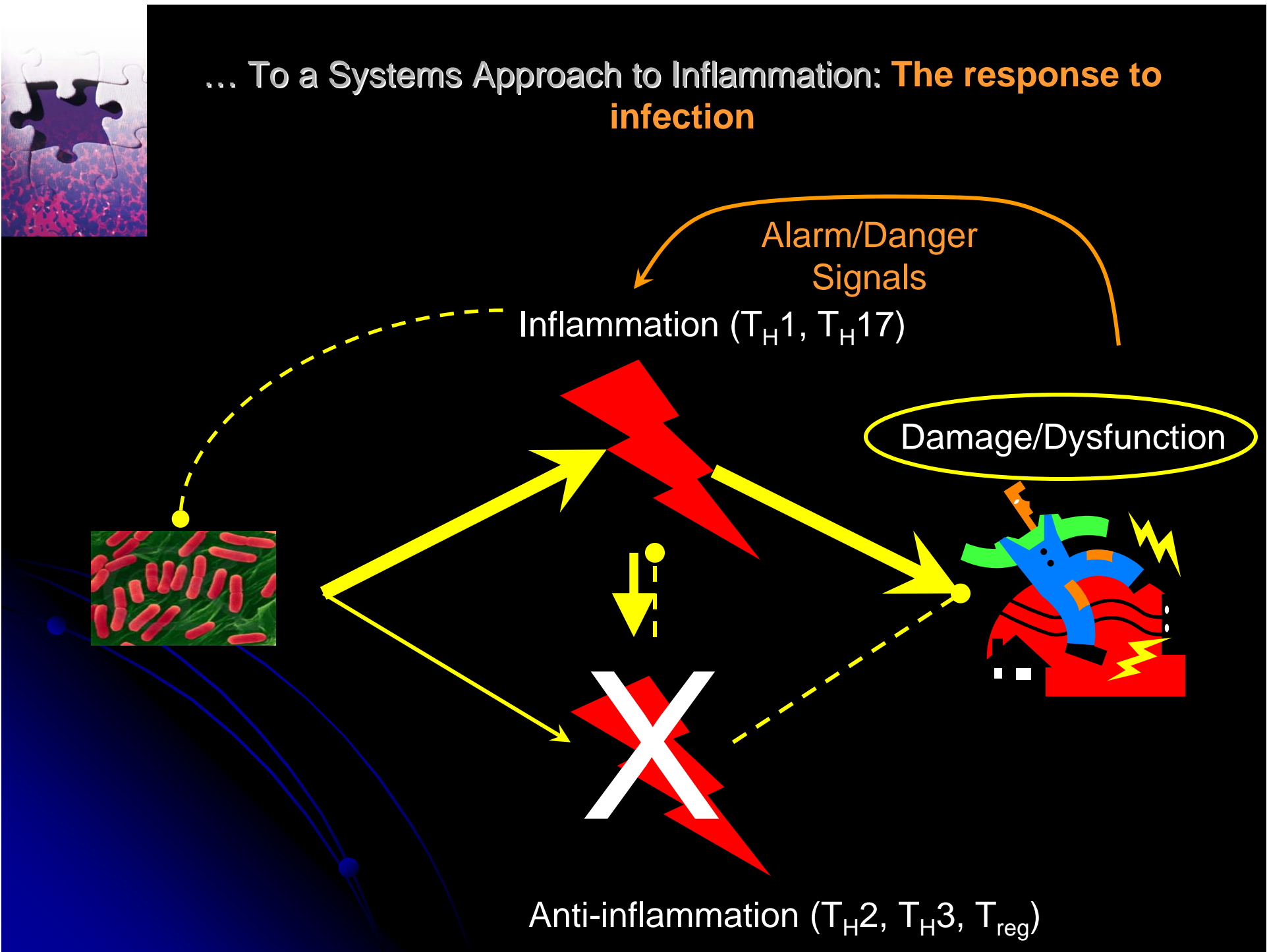


Inflammation ( $T_H1$ ,  $T_H17$ )

Alarm/Danger Signals

Damage/Dysfunction

Anti-inflammation ( $T_H2$ ,  $T_H3$ ,  $T_{reg}$ )



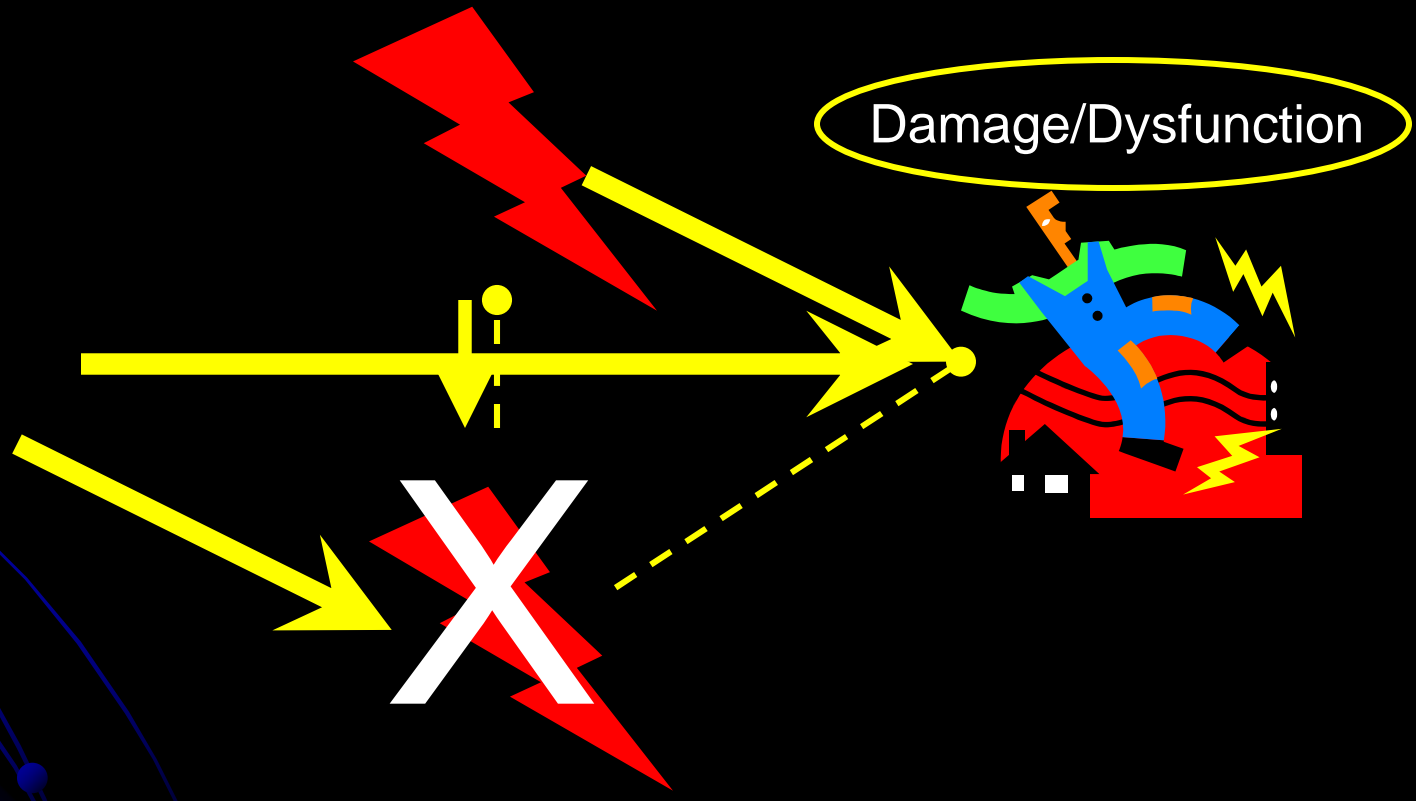


# A Systems Approach to Inflammation: **The response to trauma**

Alarm/Danger  
Signals

Inflammation ( $T_H1, T_H17$ )

Damage/Dysfunction



Anti-inflammation ( $T_H2, T_H3, T_{reg}$ )



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 Journal of Theoretical Biology 230 (2004) 145–155  
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**Journal of Theoretical Biology**  
 ELSEVIER

**The dynamics of acute inflammation**

Rukmini Kumar<sup>a</sup>, Gilles Clermont<sup>b</sup>, Yoram Vodovotz<sup>c,d</sup>, Carson C. Chow<sup>d,\*</sup>

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 Journal of Theoretical Biology 230 (2004) 145–155  
 www.elsevier.com/locate/yjtbi

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

Judy Day<sup>a</sup>, Jonathan Rubin<sup>a,\*</sup>, Yoram Vodovotz<sup>b,c,d</sup>, Carson C. Chow<sup>d</sup>, Angela Reynolds<sup>e</sup>, Gilles Clermont<sup>b,c,d</sup>

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SHOCK, Vol. 24, No. 1, pp. 74–84, 2005

**THE ACUTE INFLAMMATORY RESPONSE IN DIVERSE SHOCK STATES**

Carson C. Chow,<sup>a</sup> Gilles Clermont,<sup>b</sup> Rukmini Kumar,<sup>c</sup> Claudio Lagoa,<sup>d</sup> Zacharia Tawadrous,<sup>e</sup> David Gallo,<sup>f</sup> Binnie Betten,<sup>g</sup> John Bartels,<sup>h</sup> Gregory Constantine,<sup>i</sup> Mitchell P. Fink,<sup>j</sup> Timothy R. Billiar,<sup>k</sup> and Yoram Vodovotz<sup>l</sup>

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**Review Article**

**IN SILICO MODELS OF ACUTE INFLAMMATION IN ANIMALS**

Yoram Vodovotz,<sup>1,\*</sup> Carson C. Chow,<sup>1,†</sup> John Bartels,<sup>2</sup> Claudio Lagoa,<sup>3</sup> Jose M. Prince,<sup>4</sup> Ryan M. Levy,<sup>5</sup> Rukmini Kumar,<sup>6</sup> Judy Day,<sup>7</sup> Jonathan Rubin,<sup>8</sup> Gregory Constantine,<sup>9</sup> Timothy R. Billiar,<sup>10</sup> Mitchell P. Fink,<sup>11</sup> and Gilles Clermont<sup>12</sup>

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SHOCK, Vol. 26, No. 6, pp. 592–600, 2006

**THE ROLE OF INITIAL TRAUMA IN THE HOST'S RESPONSE TO INJURY AND HEMORRHAGE: INSIGHTS FROM A CORRELATION OF MATHEMATICAL SIMULATIONS AND HEPATIC TRANSCRIPTOMIC ANALYSIS**

Claudio E. Lagoa,<sup>a</sup> John Bartels,<sup>b</sup> Arie Baratt,<sup>c</sup> George Tseng,<sup>d</sup> Gilles Clermont,<sup>e</sup> Mitchell P. Fink,<sup>f</sup> Timothy R. Billiar,<sup>g</sup> and Yoram Vodovotz<sup>h</sup>

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Immunologic Research 2006;36(1)–3:237–245

**Deciphering the Complexity of Acute Inflammation Using Mathematical Models**



Yoram Vodovotz

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

Jose M Prince,<sup>1</sup> Ryan M Levy,<sup>2</sup> John Bartels,<sup>3</sup> Arie Baratt,<sup>4</sup> John M Kane, III,<sup>5</sup> Claudio Lagoa,<sup>6</sup> Jonathan Rubin,<sup>7,8</sup> Judy Day,<sup>9</sup> Joyce Wei,<sup>2</sup> Mitchell P Fink,<sup>1,4,5</sup> Sanna M Goyert,<sup>6</sup> Gilles Clermont,<sup>4,5</sup> Timothy R Billiar,<sup>1,5</sup> and Yoram Vodovotz<sup>1,5,7</sup>

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SHOCK, Vol. 00, No. 0, pp. 00–00, 2007

**A MATHEMATICAL SIMULATION OF THE INFLAMMATORY RESPONSE TO ANTHRAX INFECTION**

Rukmini Kumar,<sup>a</sup> Carson C. Chow,<sup>b</sup> John D. Bartels,<sup>c</sup> Gilles Clermont,<sup>d</sup> and Yoram Vodovotz<sup>e</sup>

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

Angela Reynolds<sup>a</sup>, Jonathan Rubin<sup>a,\*</sup>, Gilles Clermont<sup>b,c,d</sup>, Judy Day<sup>e</sup>, Yoram Vodovotz<sup>b,c,e</sup>, G. Bard Ermentrout<sup>f</sup>

<sup>a</sup>Department of Mathematics, 301 Thackeray, University of Pittsburgh, Pittsburgh, PA 15260, USA  
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**Review article**

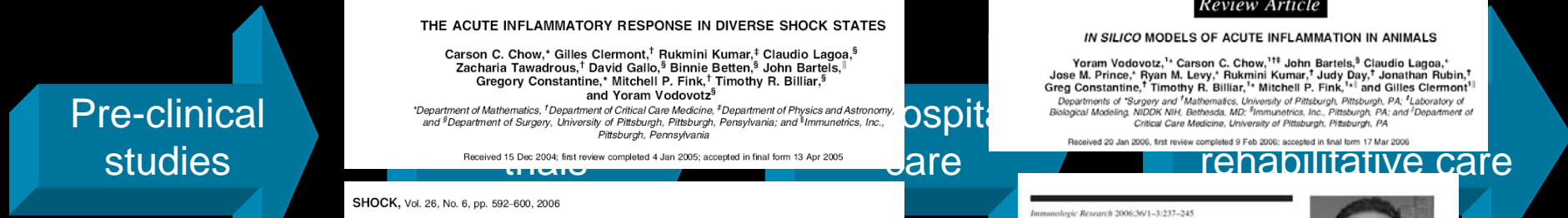
**Mathematical modeling in necrotizing enterocolitis—a new look at an ongoing problem**

Jeffrey S. Upperman<sup>a,\*</sup>, Victoria Camerini<sup>a,b</sup>, Brian Lugo<sup>a</sup>, Ivan Yotov<sup>c</sup>, Joshua Sullivan<sup>c</sup>, Joshua Rubin<sup>c</sup>, Gilles Clermont<sup>c,d</sup>, Ruben Zamora<sup>e</sup>, G. Bard Ermentrout<sup>f</sup>, Henri R. Ford<sup>g</sup>, Yoram Vodovotz<sup>b,h</sup>

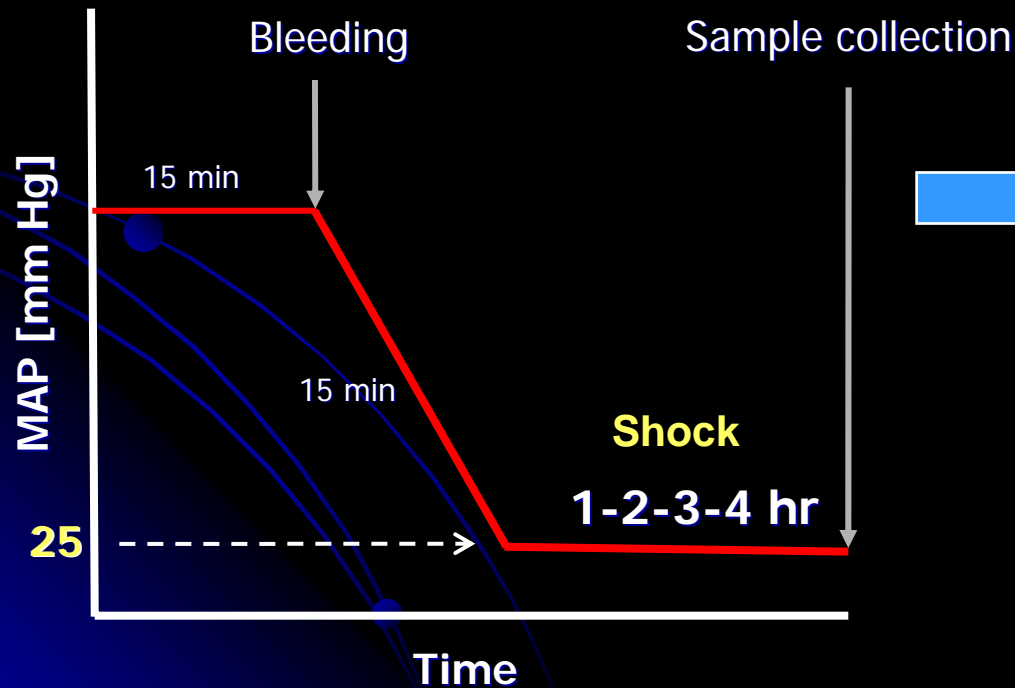
**Shock, 2008, In Press**

**Mathematical Modeling of Post-hemorrhage Inflammation in Mice: Studies Using a Novel, Computer-controlled, Closed-loop Hemorrhage Apparatus**

Andres Torres<sup>a</sup>; Timothy Bentley<sup>b</sup>; John Bartels, B.S.<sup>c</sup>; Derek Barclay<sup>d</sup>; Rajaie Namas<sup>e</sup>; Ruben Zamora<sup>a</sup>; Juan Carlos Puyana<sup>a,\*</sup>; Yoram Vodovotz<sup>a,\*†</sup>



# Apparatus for Automated, Closed-loop Hemorrhagic Shock and Resuscitation (Torres et al. Shock, In Press)

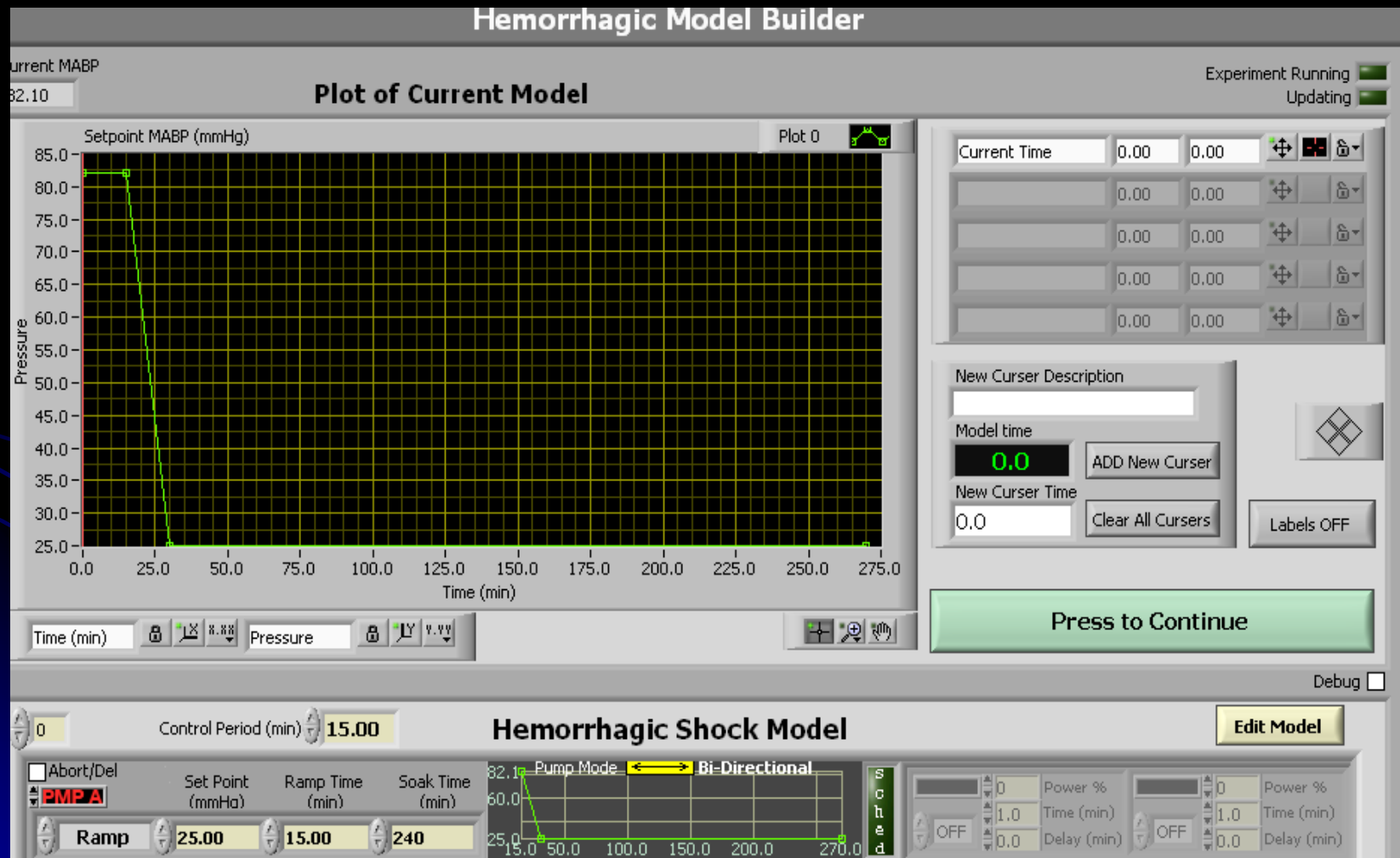


Analysis of  
Cytokines  
(Plasma)

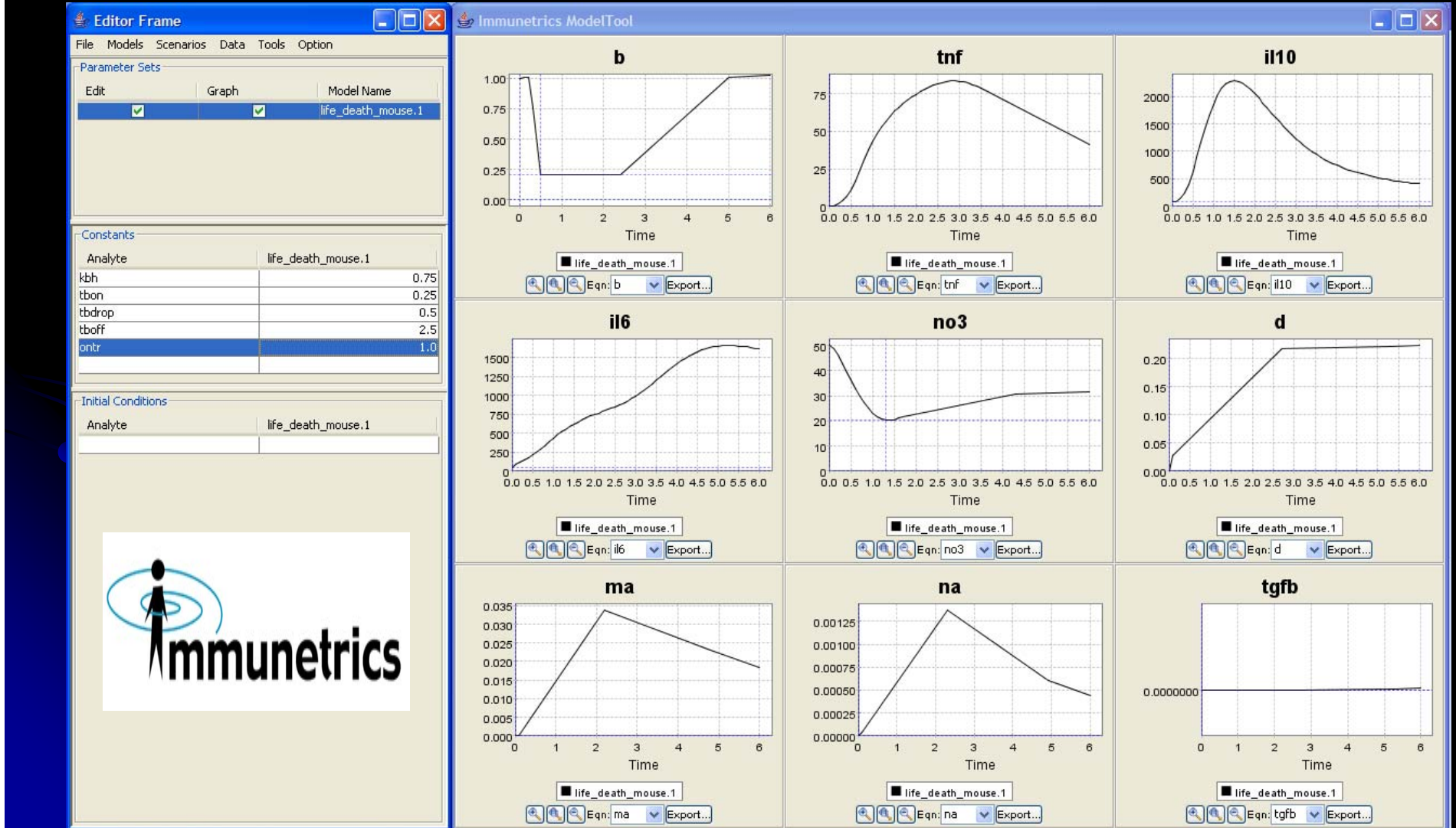
Luminex™

Data  
Analysis &  
Modeling

# Computational Control and Simulation of Hemorrhagic Shock & Resuscitation



# Computational Control and Simulation of Hemorrhagic Shock & Resuscitation



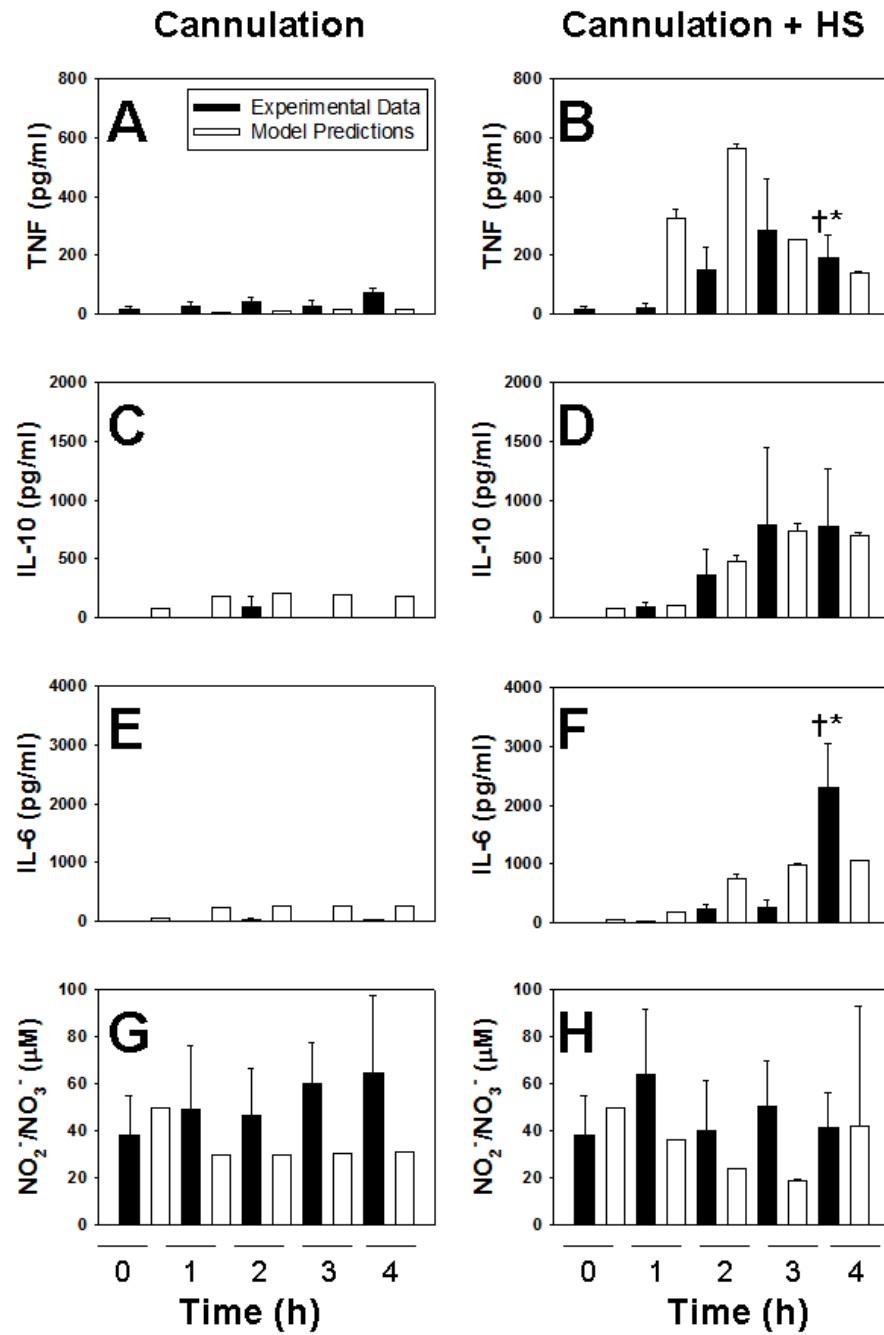


Previous model (Chow et al. Shock 2005) was calibrated on data from mice subjected to 2.5 h cannulation ± HS + various times of resuscitation.

In this study: 1-4 h of cannulation ± HS

\*p < 0.05 vs. surgical cannulation alone.

†p < 0.05 within HS treatment group.





## *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

Pre-clinical studies

SHOCK, Vol. 29, No. 1, pp. 104–111, 2008

### A MATHEMATICAL SIMULATION OF THE INFLAMMATORY RESPONSE TO ANTHRAX INFECTION

Rukmini Kumar,\* Carson C. Chow,<sup>†</sup> John D. Bartels,<sup>‡</sup> Gilles Clermont,<sup>§</sup> and Yoram Vodovotz<sup>||</sup>

Departments of \*Physics, and <sup>†</sup>Mathematics, University of Pittsburgh; <sup>‡</sup>Immunetrics, Inc; Departments of <sup>§</sup>Critical Care Medicine, and <sup>||</sup>Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania

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onic /  
tive care

Wound Repair and Regeneration

### Agent-based model of inflammation and wound healing: insights into diabetic foot ulcer pathology and the role of transforming growth factor- $\beta$ 1

Qi Mi<sup>1</sup>; Beatrice Rivière<sup>1,2</sup>; Gilles Clermont<sup>2,3</sup>; David L. Steed<sup>4</sup>; Yoram Vodovotz<sup>2,4</sup>

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2. Department of Center for Inflammation and Regenerative Modeling, McGowan Institute for Regenerative Medicine,
3. Department of Critical Care Medicine, and
4. Department of Surgery, University of Pittsburgh, Pittsburgh, PA





Pre-clinical  
studies

trials

care

rehabilitative care



## Agent-based model of inflammation and wound healing: insights into diabetic foot ulcer pathology and the role of transforming growth factor- $\beta$ 1

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3. Department of Critical Care Medicine, and
4. Department of Surgery, University of Pittsburgh, Pittsburgh, PA

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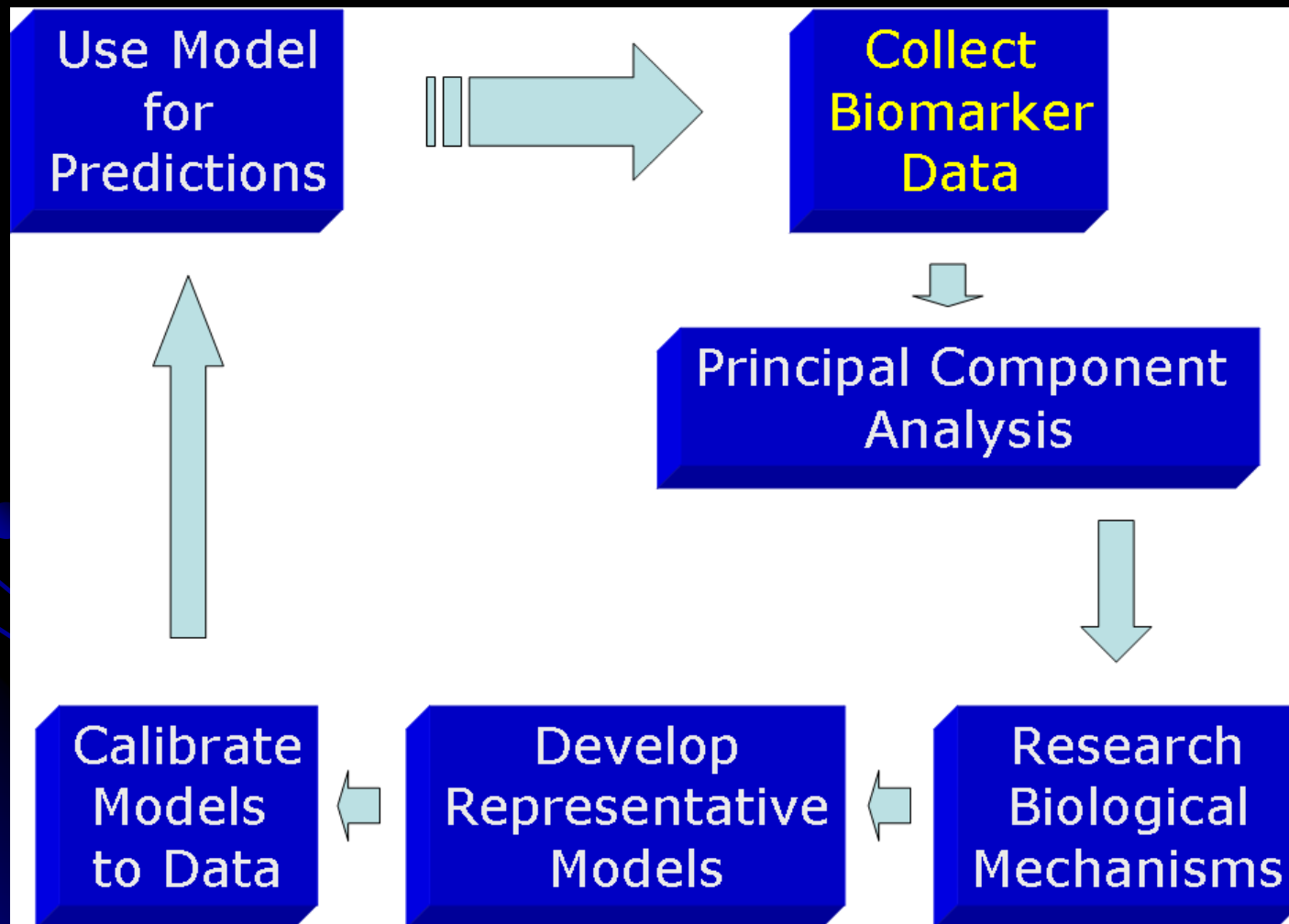
PLoS one

## A Patient-Specific *in silico* Model of Inflammation and Healing Tested in Acute Vocal Fold Injury

Nicole Y. K. Li<sup>1</sup>, Katherine Verdolini<sup>1,2,3,4,7\*</sup>, Gilles Clermont<sup>4,5,7</sup>, Qi Mi<sup>4,6,7</sup>, Elaine N. Rubinstein<sup>8</sup>, Patricia A. Hebda<sup>1,2,7,9,10</sup>, Yoram Vodovotz<sup>1,4,7,11</sup>

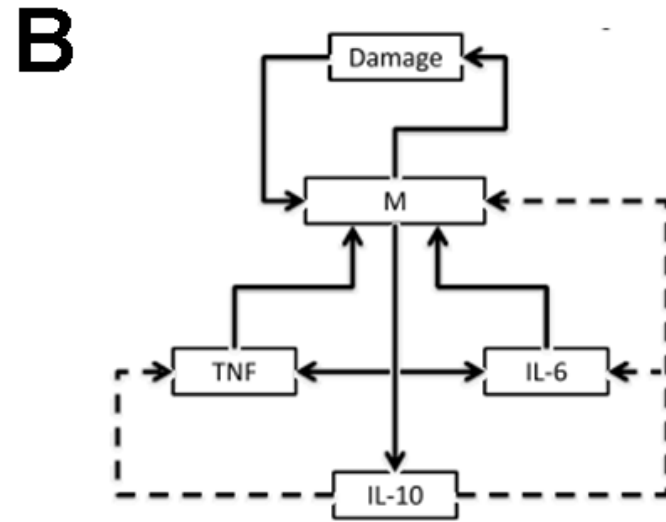
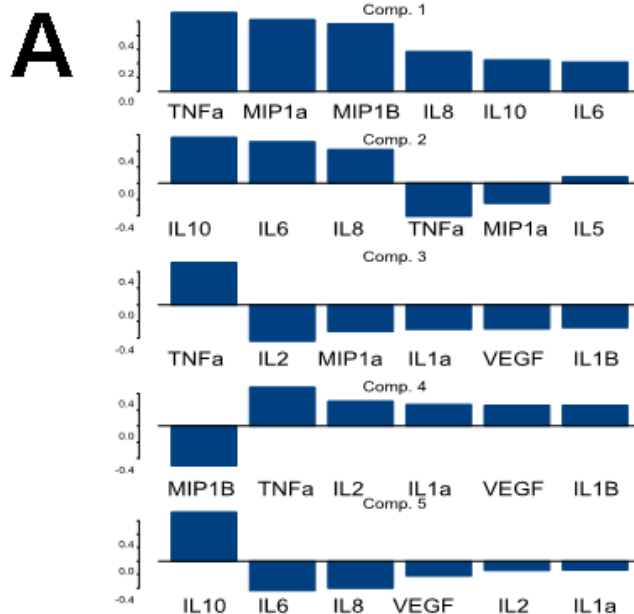
1 Department of Communication Science and Disorders, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, 2 Department of Otolaryngology, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, 3 University of Pittsburgh Voice Center, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, 4 Center for Inflammation and Regenerative Modeling, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, 5 Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, 6 Department of Sports Medicine and Nutrition, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, 7 McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, 8 Office of Measurement and Evaluation of Teaching, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, 9 Otolaryngology Wound Healing Laboratory, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, 10 Department of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, 11 Department of Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America

# Patient-specific simulations of traumatic brain injury (Okonkwo, Constantine, Solovyev, Mi)





# Patient-specific simulations of traumatic brain injury (Okonkwo, Constantine, Solovyev, Mi)



**C**

$$\frac{dD}{dt} = d_0 M - d_1 D$$

$$\frac{dM}{dt} = \left( \frac{m_0 D}{1 + m_1 D} + \frac{m_2 C}{1 + m_3 C} + \frac{m_4 \text{TNF}}{1 + m_5 \text{TNF}} + \frac{m_6 \text{IL}_6}{1 + m_7 \text{IL}_6} \right) \frac{1}{1 + m_8 \text{IL}_{10}} - m_9 M$$

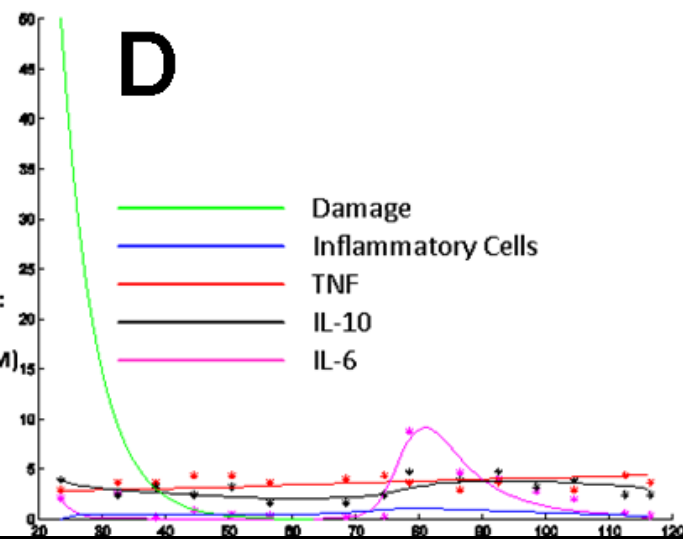
$$\frac{dC}{dt} = \frac{c_0 D}{1 + c_1 D} - c_2 C$$

$$\frac{d\text{IL}_{10}}{dt} = i_0 M - i_1 \text{IL}_{10}$$

$$\frac{d\text{TNF}}{dt} = \frac{t_0 M}{1 + t_1 \text{IL}_{10}} - t_2 \text{TNF}$$

$$\frac{d\text{IL}_6}{dt} = \frac{b_0 M^6}{1 + b_1 \text{IL}_{10}} - b_2 \text{IL}_6$$

**Terms in the model:**  
 Damage (D)  
 Inflammatory cell (M)  
 Chemokine (C)  
 IL-10 (IL<sub>10</sub>)  
 TNF (TNF)  
 IL-6 (IL<sub>6</sub>)





**Main problem:** time required for inflammation assays and personalized modeling may be too slow for effective therapy for fast-evolving inflammatory processes

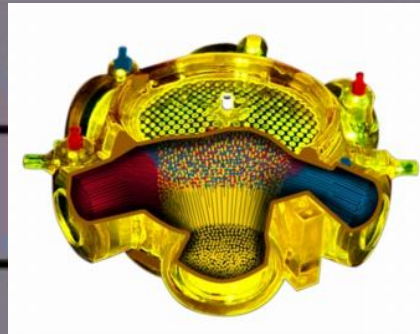
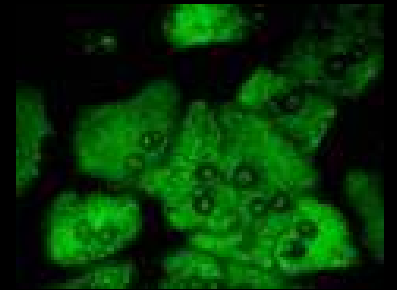
## Patient-specific, inflammation-regulating bioreactor

Provisional patent application: “Self-Regulating Device for Modulating Inflammation.”  
(Serial No. 61/100,845)



**CYTOKINE  
PROMOTER**

**ENDOGENOUS INHIBITOR**



**Inflammation-Regulating Bioreactor**

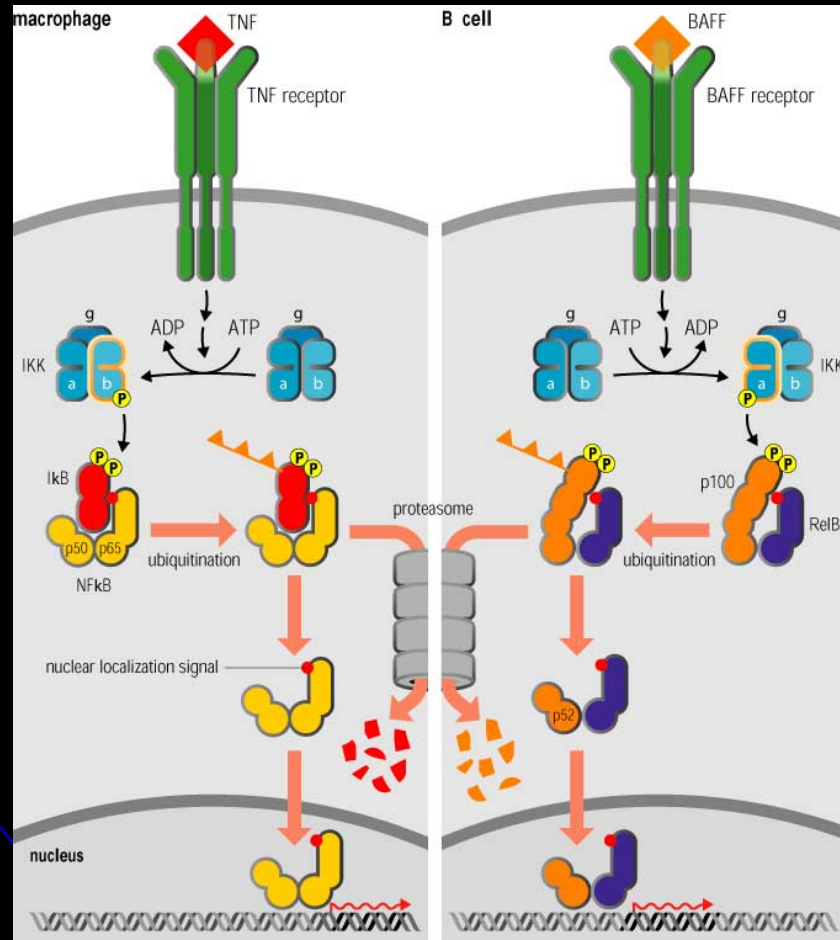
**Benefits:**

- Single device for FDA
- Self-regulating
- Response can be tuned
- Modular
- Infinitely modifiable
- Designed using mathematical model to be disease/stage-specific

**Uses:**

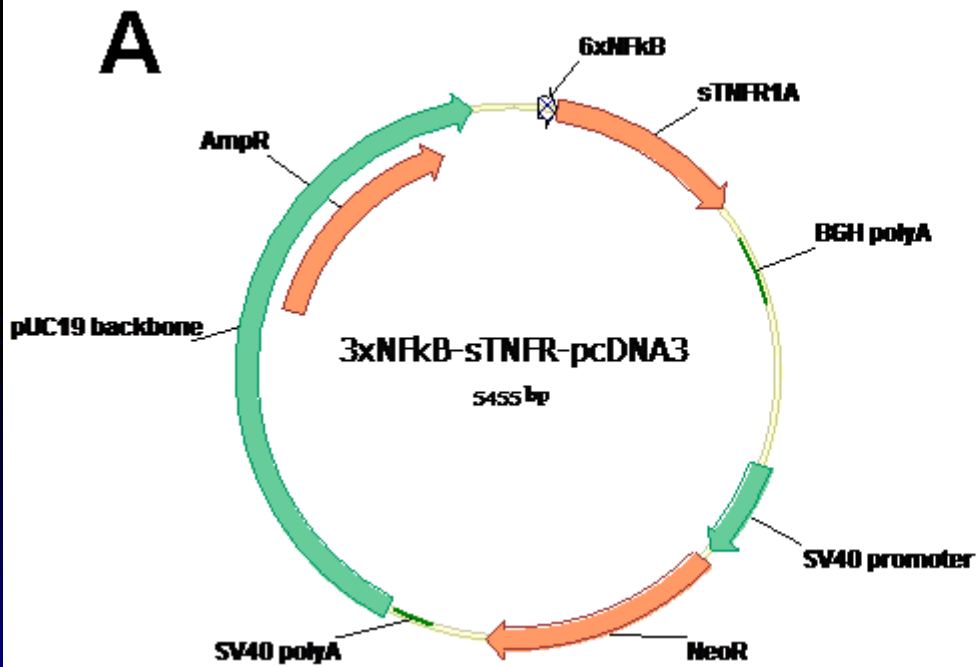
- Sepsis
- Trauma
- Chronic diseases
- Wound healing
- Cancer?

# Molecular Design of Negative Feedback Circuit

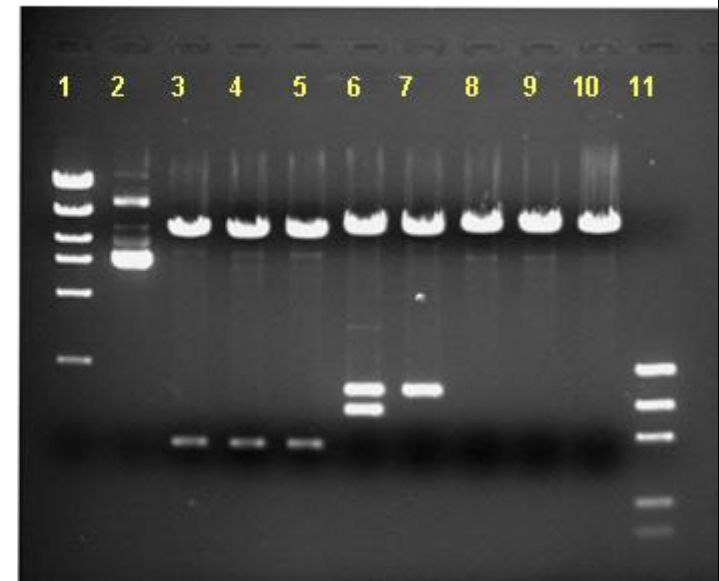


[www.stat.rice.edu/~siefert/Research/NfKB.html](http://www.stat.rice.edu/~siefert/Research/NfKB.html)

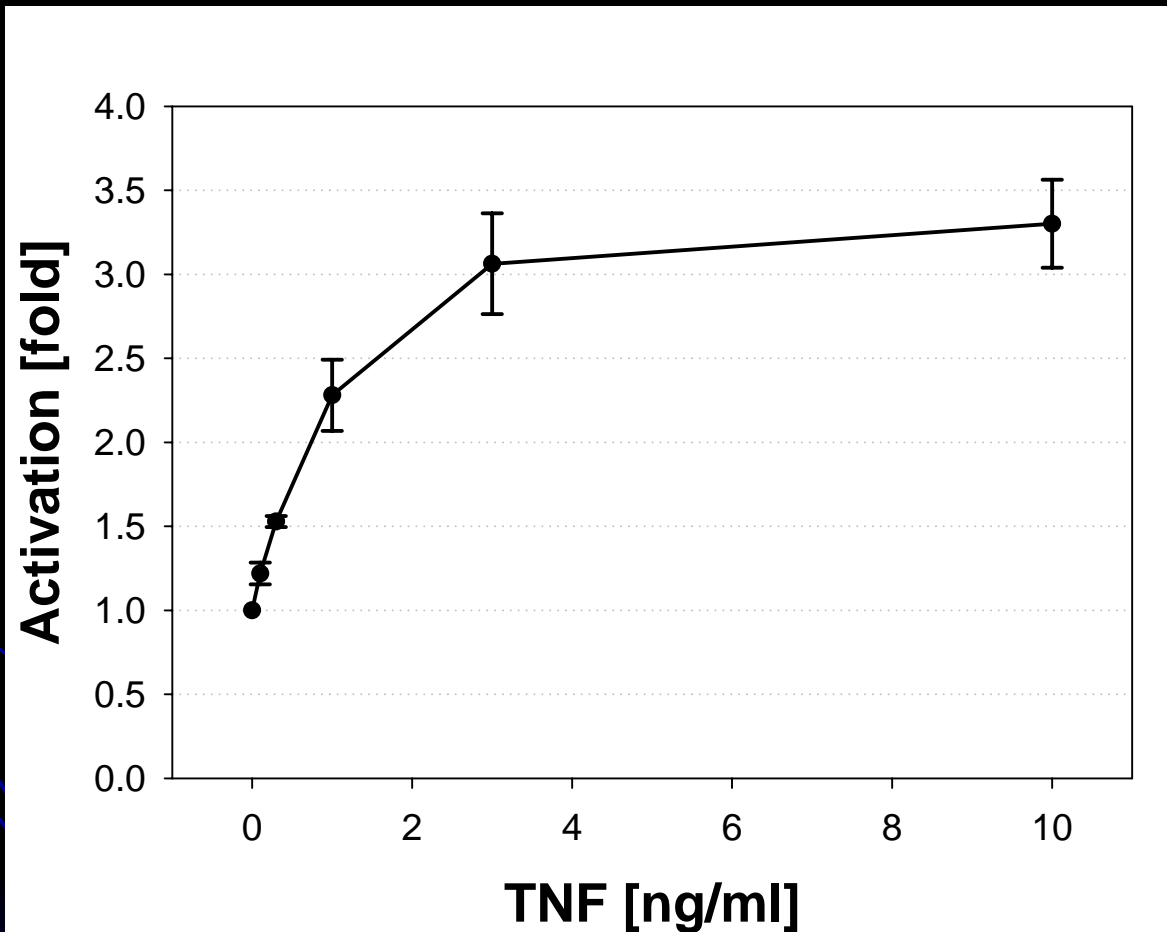
# Molecular Design of Negative Feedback Circuit



**B**



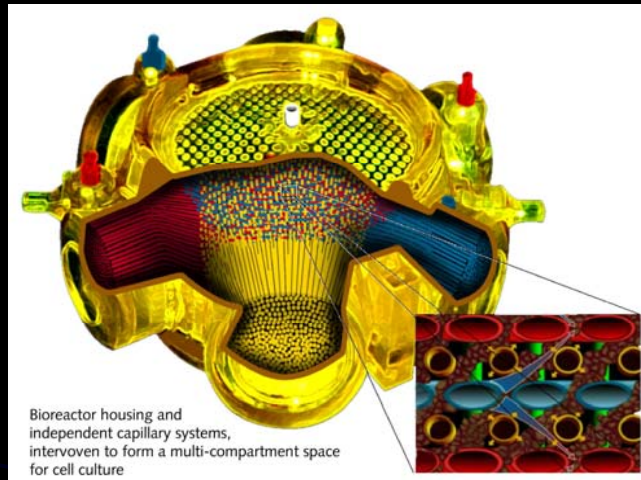
# Production of sTNFR by Modified HepG2 Cells as a Function of TNF Dose



n = 3



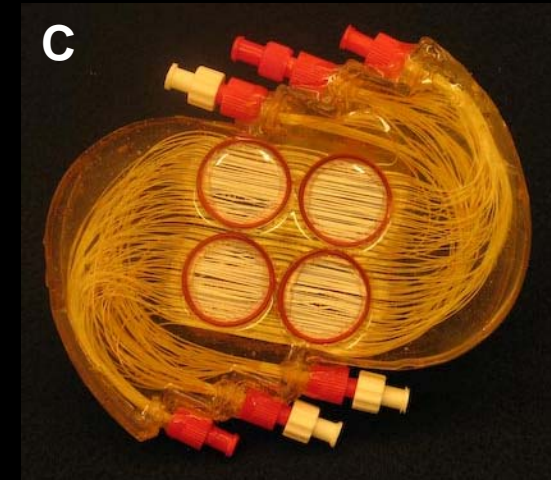
# Liver Bioreactors



8 mL



2 mL



1 mL

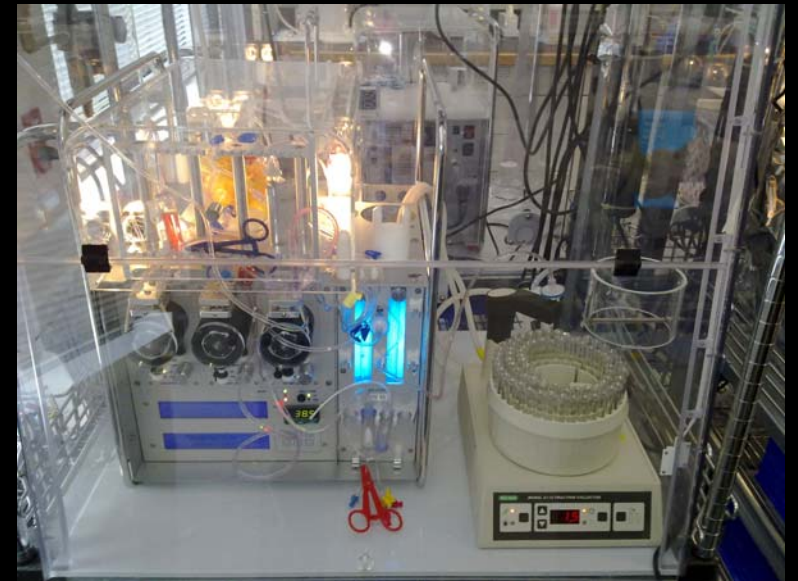
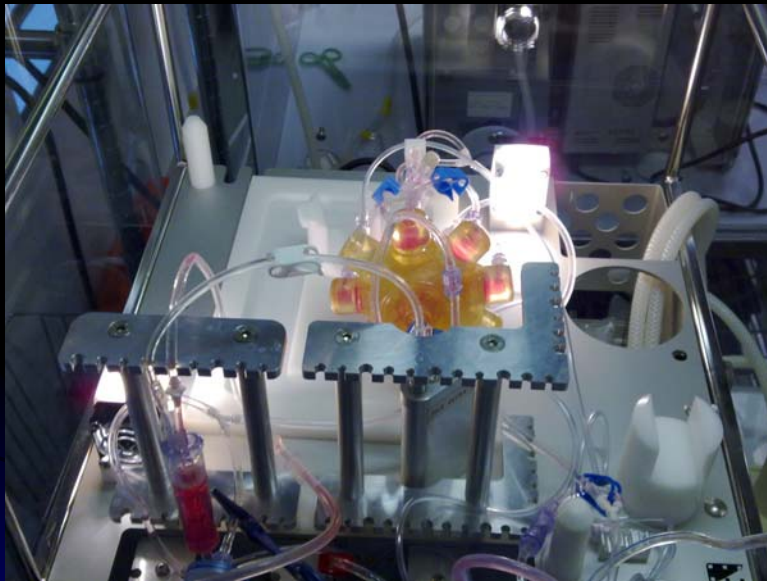
Two independent, interwoven fiber bundles are interwoven for culture medium transport (red and blue) with one fiber bundle for gas transport (yellow).

Cells reside in the interstitial spaces between the fibers (inset).

Courtesy of J. Gerlach, University of Pittsburgh

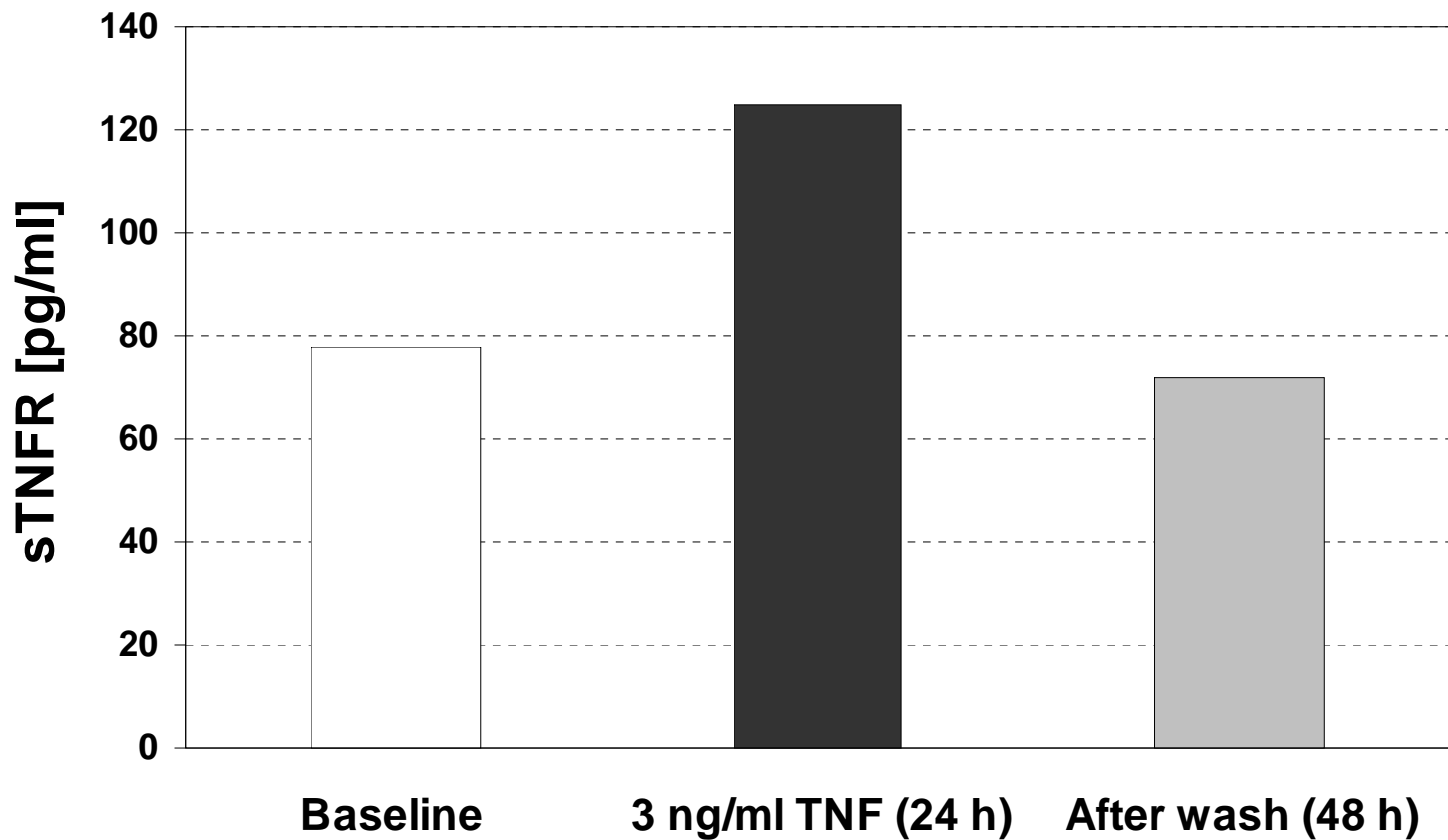


# The First Bioreactor Experiment...



Maxim Mikheev, in collaboration with Jörg Gerlach's lab, using transiently transfected HepG2 cells in 8-mL bioreactor

# The First Bioreactor Experiment...



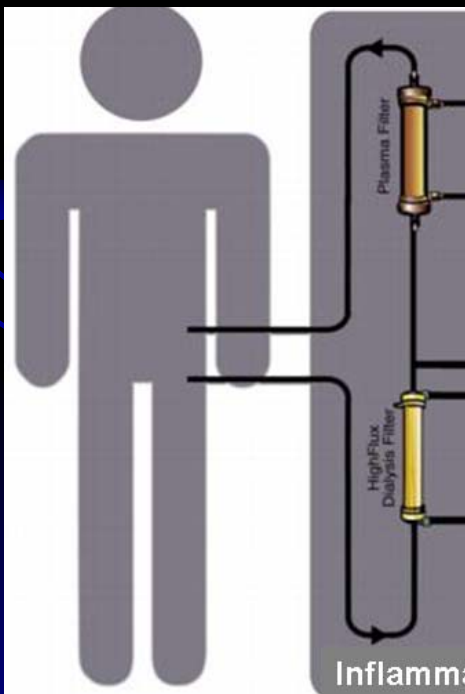
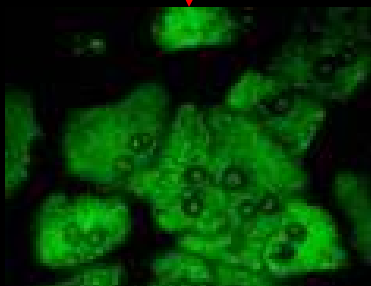


**CYTOKINE PROMOTER**

**FLUORESCENT PROTEIN**

**CYTOKINE PROMOTER**

**ENDOGENOUS INHIBITOR**



**Inflammation-Regulating Theranostic**



# Summary

- We have created an array of computational simulations of the inflammatory and intertwined damage / healing response
- To gain translational insights into hemorrhage & resuscitation, we have constructed an automated, closed-loop, computer controlled platform that allows for highly accurate, reproducible, and mathematically predictable hemorrhagic shock in mice
- We have utilized these simulations for *in silico* clinical trials, patient-specific “smart” diagnostics, and rational device design, culminating in a prototype inflammation-regulating bioreactor
- Next step: studies in mice using closed-loop system



# Funding and Other Support

- National Institutes of Health
- National Institute on Disability Rehabilitation Research
- Commonwealth of Pennsylvania
- Department of Defense / Pittsburgh Tissue Engineering Initiative
- Pittsburgh Lifesciences Greenhouse
- IBM