Department of Surgery University of Pittsburgh

- 1st Fulltime Chair
- Established a Faculty
- Reorganized Residency
- Leader in Clinical Excellence and Innovation
- Premiere Surgical Residency
- Tradition of Excellence in Surgical Research
- Specialization and Growth of Faculty
Grand Canyon swim  Mt. Everest climb
Department of Surgery University of Pittsburgh Highlights

- **1950**: Samuel Harbison, M.D.
  - 1st kidney transplant in Pennsylvania

- **1960**: Henry Bahnson, M.D.
  - Theories on breast cancer
  - Formation of NSABP

- **1970**: Ravitch
  - Introduces stapling techniques into American Surgery

- **1980**: Starzl arrives Pitt
  - Becomes the nation's leading transplant center

- **1990**: T.E. Starzl Transplant Institute established

- **2000**: Simmons
  - Billiar Geller: Discoveries in NO research
  - Luketich Makaroun Schauer
  - Innovations in minimally invasive surgery

- **2000**: Starzl awarded the National Science Medal

- **1950-2000**

- **1950-2000**: Marcia leads transplant team in performing over 850 organ transplants

- **1970-2000**: McCurry
  - 1st program to exceed 100 lung transplants in a single year
Department of Surgery
University of Pittsburgh
Overview

• Faculty: 197

• Academic Divisions:
  General surgery (A. Peitzman)
  Thoracic (J. Luketich)
  Cardiac (K. Zehr)
  Pediatric (G. Gittes)
  Plastics (A. Lee)
  Surgical Oncology (D. Bartlett)
  Transplantation (A. Marcos)
  Vascular (M. Makaroun)

• Over 82,000 procedures

• Clinical revenues: 45 million

• Hospitals:
  Presbyterian University Hospital
  Montefiore University Hospital
  VA Hospital
  Childrens Hospital of Pittsburgh
  Shadyside Hospital/Hillman Cancer Center
  Magee Womens Hospital
  St Margarets Hospital
  Passavant Hospital
  McKeesport Hospital
  Baddock Hospital
  Southside Hospital
## Department Highlights—Academic:

### Faculty Recognition
- Lasker Award recipient
- National Science Medal recipient
- Members Institute of Medicine: 4

### Research Funding (20–25 million)
- Consistently in the top 5 for NIH funding
- 4 NIH training grants

### Academic Institutes
- T.E. Starzl Transplant Institute
- McGowan Institute for Regenerative Medicine

### Endowed Chairs / Professorships: 17

### Society of University Surgeons Presidents: 4
## Resident Research Awards

<table>
<thead>
<tr>
<th>RESIDENT</th>
<th>AWARD</th>
<th>YEARS</th>
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<tbody>
<tr>
<td>Raja Mahidhara</td>
<td>Thoracic Surgery Foundation Award</td>
<td>2000-02</td>
</tr>
<tr>
<td>Joy Collins</td>
<td>Surgical Infection Society Resident Award</td>
<td>2000-01</td>
</tr>
<tr>
<td>Douglas Potoka</td>
<td>NIH NRSA</td>
<td>2000-01</td>
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<tr>
<td>Kaye Reid</td>
<td>Surgical Infection Society Resident Fellowship</td>
<td>2001-03</td>
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<td>Kathleen Raman</td>
<td>American College of Surgeons Resident Award</td>
<td>2002-04</td>
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<td>Eric Marderstein</td>
<td>American Society for Transplant Surgery Fellowship</td>
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<td>Vu Nguyen</td>
<td>Plastic Surgery Education Foundation Award</td>
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<td>Allan Tsung</td>
<td>American College of Surgeons Resident Award</td>
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<td>Jose Prince</td>
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<td>Geetha Jeyabalan</td>
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<td>Kevin Mollen</td>
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<td>Raghuvieer Vallabhaneni</td>
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<tr>
<td>Rahul Anand</td>
<td>Surgical Infection Society Resident Fellowship</td>
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<td>Steven Gribar</td>
<td>American College of Surgeons Resident Award</td>
<td>2006-08</td>
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<td>Mario Solario</td>
<td>NIH NRSA</td>
<td>2006-08</td>
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<td>David Kaczorowski</td>
<td>American College of Surgeons Resident Award</td>
<td>2006-08</td>
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<tr>
<td>Rebecca Edmunds</td>
<td>Society of University Surgeons Resident Award</td>
<td>2007-08</td>
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<td>YEAR</td>
<td>Standard Score</td>
<td>Percentile</td>
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<td>------</td>
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<td>2001</td>
<td>542.31</td>
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<td>2002</td>
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<td>2004</td>
<td>546.62</td>
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<td>2005</td>
<td>557.25</td>
<td>73.06</td>
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<table>
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<th>%Correct</th>
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<td>2006</td>
<td>73.50</td>
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</table>
Cardiac Surgery Division:

Chief: Kenton Zehr

M. Zenati:
- Development of an articulated robot for epicardial interventions

R. Kormos/ A. Patel:
- Bone marrow derived stem cells for cardiac regeneration

K. McCurry:
- Methods to improve lung allograft preservation

V. Morel:
- Development of a pediatric artificial heart
Thoracic Surgery Division:

Chief: Jim Luketich

J. Luketich:
- Molecular staging of esophageal cancer

V. Donenberg:
- Mechanisms of tumor chemo-resistance
Plastic Surgery Division:

Chief: Andrew Lee

A. Lee:
- Composite tissue allograft research

P. Rubin:
- Adipose-derived stem cells for tissue regeneration
Vascular Surgery Division:

Chief: Michel Makaroun

D. Vorp:
- Bioengineering new blood vessels
- Biomechanics of abdominal aortic aneurysms

E. Tzeng:
- Therapies to prevent injury-induced intimal hyperplasia

M. Bauer:
- Mechanisms of vascular remodelling
Pediatric Surgery Division:

Chief: George Gittes

G. Gittes:
- Extracellular signals involved in pancreatic development

D. Hackam:
- Mechanisms of neonatal gut injury - Necrotizing enterocolitis

J. Fuchs:
- Characterization of stem cells in neuroblastoma
Surgical Oncology Division:

Chief: David Bartlett

UPCI-based

D. Bartlett:
- Development of oncolytic vaccinia viruses to treat cancer
- Hyperthermic hepatic chemoperfusion for metastatic liver disease

M. Lotze:
- The connection between inflammation and cancer

Y. Lee:
- Studies on the metabolic characteristics of tumor cells
- Mechanisms of hepatic metastasis

P. Kalinski:
- DC-based immunotherapy to treat cancer

A. Gambotto:
- Adenovirus-based vaccines
- Adenoviral vector core

Andy Amoscato:
- Role of ceramide in radiation induced injury
Surgical Oncology Division:

Chief: David Bartlett

PUH-based

J. Yim:
-Mechanisms of interferon and IRF-1 tumor killing

S. Hughes:
-Mechanisms of tumor cell escape from apoptosis
General Surgery Division:

Chief: Andrew Peitzman

Trauma/ Acute Care Surgery-PUH

T. Billiar:
-Mechanisms of injury-induced inflammation
-Mechanism of end organ-induced injury in sepsis and shock

Y. Vodovotz:
-Computational modeling of acute illness

J. Ochoa:
-Immune suppressor cell function following injury

M. Rosengart:
-Calcium-mediated signaling in sepsis

B. Zuckerbraun:
-Protective actions of heme oxygenase/ CO in acute injury
General Surgery Division:

Chief: Andrew Peitzman

Trauma/ Acute Care Surgery-VA

M. Wilson:
- Development of tissue oxygen sensors to optimize resuscitation

J. Fan:
- Mechanisms of acute lung injury following shock
General Surgery Division:

Chief: Andrew Peitzman

Bariatric surgery

A. Courcoulas:
- Outcomes research in bariatric surgery
Genesis: Recognition that junior faculty struggle to get first funding and convert K-funding to R-funding

Goal: Provide team mentoring from a group experienced clinician investigators (Simmons, Lotze, Billiar, Gittes) to junior faculty.

Format: Monthly 90 min meetings where faculty member presents a short- and long-term plan or progress report. Attendees include other junior faculty at the same stage.
The Molecular Biology of Traumatic/ Hemorrhagic Shock

Trauma Research Center
University of Pittsburgh

Program Director:
Timothy R. Billiar, MD

Project/core Leaders:
Mitch Fink, MD (CCM)
Tony Bauer, PhD (Medicine)
Bruce Pitt, PhD (EOH-GSPH)
Juan Ochoa, MD (Surgery)
Yoram Vodovotz, PhD (Surgery)
Simon Watkins, PhD (Cell Biology)

Affiliated investigators:
David Hackam, MD, PhD (Surgery)
Matthew Rosengart, MD, MPH (Surgery)
Andrew Peitzman, MD (Surgery)
Claudio Lagoa, DVM (Surgery)
Mazen Zenati, MD, PhD (Surgery)

NIH Center Grant
#P50-GM-53789
7/97-6/09
<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause of Death</th>
<th>Number of Deaths</th>
<th>Percent(%) of Total Deaths</th>
<th>Death Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Heart diseases</td>
<td>685,089</td>
<td>28.0</td>
<td>231.6</td>
</tr>
<tr>
<td>2</td>
<td>Cancer</td>
<td>556,902</td>
<td>22.7</td>
<td>190.1</td>
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<tr>
<td>3</td>
<td>Cerebrovascular diseases</td>
<td>157,689</td>
<td>6.4</td>
<td>53.3</td>
</tr>
<tr>
<td>4</td>
<td>Chronic lower respiratory diseases</td>
<td>126,382</td>
<td>5.2</td>
<td>43.3</td>
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<tr>
<td>5</td>
<td>Accidents (unintentional injuries)</td>
<td>109,277</td>
<td>4.5</td>
<td>37.2</td>
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<tr>
<td>6</td>
<td>Diabetes mellitus</td>
<td>74,219</td>
<td>3.0</td>
<td>25.3</td>
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<tr>
<td>7</td>
<td>Influenza &amp; pneumonia</td>
<td>65,163</td>
<td>2.7</td>
<td>21.9</td>
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<td>8</td>
<td>Alzheimer disease</td>
<td>63,457</td>
<td>2.6</td>
<td>21.3</td>
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<tr>
<td>9</td>
<td>Nephritis, nephrotic syndrome, &amp; nephrosis</td>
<td>42,453</td>
<td>1.7</td>
<td>14.4</td>
</tr>
<tr>
<td>10</td>
<td>Septicemia</td>
<td>34,069</td>
<td>1.4</td>
<td>11.6</td>
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<tr>
<td>11</td>
<td>Intentional self-harm (suicide)</td>
<td>31,484</td>
<td>1.3</td>
<td>10.7</td>
</tr>
<tr>
<td>12</td>
<td>Chronic liver disease &amp; cirrhosis</td>
<td>27,503</td>
<td>1.1</td>
<td>9.3</td>
</tr>
<tr>
<td>13</td>
<td>Hypertension and hypertensive renal disease</td>
<td>21,940</td>
<td>0.9</td>
<td>7.4</td>
</tr>
<tr>
<td>14</td>
<td>Parkinson disease</td>
<td>17,997</td>
<td>0.7</td>
<td>6.1</td>
</tr>
<tr>
<td>15</td>
<td>Assault (homicide)</td>
<td>17,732</td>
<td>0.7</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>All other &amp; ill-defined causes</td>
<td>416,932</td>
<td>17.0</td>
<td></td>
</tr>
</tbody>
</table>

*Rates are per 100,000 population and age-adjusted to the 2000 US standard population.

Note: Percentages may not total 100 due to rounding. Symptoms, signs, and abnormalities, events of undetermined intent, and pneumonitis due to solids and liquids were excluded from the cause of death ranking order.

## Ten Leading Causes of Death

**By Age and Sex, United States, 2003**

### Ages 20–39

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Causes</strong></td>
<td>65,307</td>
<td>30,021</td>
</tr>
<tr>
<td>1 Accidents (unintentional injuries)</td>
<td>21,509</td>
<td>7,044</td>
</tr>
<tr>
<td>2 Intentional self-harm (suicide)</td>
<td>8,662</td>
<td>5,206</td>
</tr>
<tr>
<td>3 Assault (homicide)</td>
<td>7,912</td>
<td>2,725</td>
</tr>
<tr>
<td>4 Heart diseases</td>
<td>5,575</td>
<td>2,725</td>
</tr>
<tr>
<td>5 Cancer</td>
<td>4,415</td>
<td>1,862</td>
</tr>
<tr>
<td>6 HIV disease</td>
<td>2,828</td>
<td>1,670</td>
</tr>
<tr>
<td>7 Diabetes mellitus</td>
<td>867</td>
<td>1,307</td>
</tr>
<tr>
<td>8 Chronic liver disease &amp; cirrhosis</td>
<td>833</td>
<td>687</td>
</tr>
<tr>
<td>9 Cerebrovascular diseases</td>
<td>790</td>
<td>619</td>
</tr>
<tr>
<td>10 Influenza &amp; pneumonia</td>
<td>511</td>
<td>424</td>
</tr>
<tr>
<td>11 Chronic liver disease &amp; cirrhosis</td>
<td>420</td>
<td>420</td>
</tr>
</tbody>
</table>
The Inflammatory Response Following Trauma

- **Hyperinflammation**
  - Traumatic Insult
  - 0-48 hrs

- **Early MOF**
  - SIRS
  - Days to weeks

- **CARS**
  - Excessive Immunosuppression

- **Late MOF** (Sepsis)

- **Resolution**
The Inflammatory Response Following Trauma

Hyperinflammation

Early MOF

Days to weeks

Resolution

Late MOF (Sepsis)

Excessive Immunosuppression

O-48 hrs

Traumatic Insult
Defining the Initiating Events

Study Approach

1. Define the inflammatory signaling pathways after injury
2. Define the initial changes in gene expression after injury

Generate hypotheses: Identify therapeutic targets

Test in animal models

Build a mathematical model
Defining the Initiating Events

**Study Approach**

1. Define the inflammatory signaling pathways after injury
2. Define the initial changes in gene expression after injury

Generate hypotheses: Identify therapeutic targets

- Test in animal models
- Build a mathematical model

**Goal:**
- Clinical trials
- New resuscitation strategies
RESULTS USING ANOVA/K-MEANS CLUSTERING

Injury= Bilateral femor fracture+1.5 hr Hemorrhagic Shock

DIFFERENTIALLY EXPRESSED FUNCTIONS - LIVER

IPA top functions

1. cell death/growth & proliferation/inflammation
2. immune response/cell death/growth & proliferation
3. cell movement/ immune response/ cell death/growth & proliferation
4. cell death/growth and proliferation
5. cell cycle/growth and proliferation/signaling
6. cell death/immune response/immune system development
7. cell death/cell cycle/growth & proliferation
8. gene expression/cell death/cell morphology
9. cell to cell signaling/cell cycle/immune system development
10. cell death/cell cycle/cell signaling/molecular transport
11. cell death/cell cycle/gene expression
12. cell cycle/connective tissue disorders/immune function/DNA repair
13. cell growth & proliferation/cell cycle/connective tissue development
14. cell growth & proliferation/cell cycle/cell movement
15. cell cycle/gene expression/growth & proliferation/immune function
16. cell assembly & organization/cell cycle/signaling/metabolism
17. cell to cell signaling/cell death/cell cycle/metabolism
18. metabolism/growth & proliferation/immune response/signaling
19. metabolism/mol. Transport/protein trafficking/cell signaling
20. metabolism/mol.transport/cell signaling/cell organization
IPA: Early Clusters’ Highest Scored Merged-Networks

The network represents genes and pathways that comprise the early hepatic response after injury and shock (ischemic phase). Key to this time-point are some extracellular effectors (IL6, IL10, TNF, chemokines) and the transcription factors JUN, RELA and ATF3.

Shock 1.5 hr + bilateral femur fracture
Clinical Observation

Infection → Microbes or Microbial Products

? → Systemic Inflammatory Response

Systemic Inflammatory Response = Activation of Innate Immunity
# Toll-Like Receptor Specificity

<table>
<thead>
<tr>
<th>Mammalian Toll-Like Receptor</th>
<th>Microbial Molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR1</td>
<td>Triacyl Lipopeptides</td>
</tr>
<tr>
<td>TLR2</td>
<td>Lipoproteins</td>
</tr>
<tr>
<td></td>
<td>Peptidoglycan</td>
</tr>
<tr>
<td></td>
<td>Lipoteichoic Acid</td>
</tr>
<tr>
<td></td>
<td>Lipoarabinomannan</td>
</tr>
<tr>
<td></td>
<td>Glycoininitolphospholipids</td>
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<tr>
<td></td>
<td>Porins, Glycolipids</td>
</tr>
<tr>
<td></td>
<td>Some Lipopolysaccharides</td>
</tr>
<tr>
<td></td>
<td>Zymosan</td>
</tr>
<tr>
<td>TLR3</td>
<td>Double Stranded RNA</td>
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<td>TLR4</td>
<td>Lipopolysaccharide</td>
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<td>Envelope Protein</td>
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<td>TLR5</td>
<td>Flagellin</td>
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<td>TLR6</td>
<td>Diacyl Lipopeptides</td>
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<td>TLR8</td>
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<td>TLR9</td>
<td>CpG-Containing DNA</td>
</tr>
<tr>
<td>TLR10</td>
<td></td>
</tr>
<tr>
<td>TLR11</td>
<td>Uropathic bacteria</td>
</tr>
</tbody>
</table>

**Pathogen-associated Molecular Patterns (PAMPs):**

Molecules expressed or released by invading microorganisms that are structurally unique to the pathogen.
Clinical Observation

Infection → PAMPs
PAMPs → PRRs
PAMPs → Systemic Inflammatory Response
Systemic Inflammatory Response → Organ Dysfunction

Infection → Organ Dysfunction

Injury → Organ Dysfunction

Systemic Inflammatory Response → Organ Dysfunction

Infection, PAMPs, PRRs, Systemic Inflammatory Response, Organ Dysfunction
Classes of Molecules That Initiate The Innate Immune Response

*Pathogen-associated Molecular Patterns (PAMPs):*

Exogenous molecules expressed or released by invading microorganisms that are structurally unique to the pathogen.

*Damage-associated Molecular Patterns (DAMPs):*

Endogenous molecules that are normally unavailable to the immune system that are released and recognized by immune cells following tissue injury.
Sources of Endogenous Danger Signals
(Damage Associate Molecular Pattern (DAMP) Molecules)

1. Damaged or Dying Cells
2. Secreted From Stressed Cells
3. Degradation of Tissue Matrix
4. Protease
5. PMN

DAMPs → Pattern Recognition Receptor
# Toll-Like Receptor Specificity

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<td>TLR2</td>
<td>Lipoproteins</td>
<td>Heat Shock Protein 70</td>
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<tr>
<td></td>
<td>Peptidoglycan</td>
<td>HMGB1</td>
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<td>Double Stranded RNA</td>
<td>mRNA</td>
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<td>TLR4</td>
<td>Lipopolysaccharide</td>
<td>Heat Shock Proteins</td>
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<td>Fusion Protein</td>
<td>Fibronectin (Domain A)</td>
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<td>Hyaluronan</td>
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<td>Fragment of Heparin Sulfate</td>
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<td></td>
<td></td>
<td>Fibrinogen</td>
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<td></td>
<td></td>
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<td>mRNA</td>
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<td>Fusion Protein</td>
<td>Fibronectin (Domain A)</td>
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<td>Fibrinogen</td>
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<td>HMGB1</td>
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<td>TLR5</td>
<td>Flogellin</td>
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<td>Diacyl Lipopeptides</td>
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<td>Single Stranded RNA</td>
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<td>TLR8</td>
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<tr>
<td>TLR9</td>
<td>CpG-Containing DNA</td>
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<td>TLR10</td>
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<tr>
<td>TLR11</td>
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Toll-like Receptor 4

TLR4 modulates the inflammatory response in models of sterile inflammation

Endogenous Molecules Released from stressed or damaged tissues (DAMPs)

LPS

CD14

MD-2

NF-κB Activation

Expression of Inflammatory Cytokines

Induction of IFN-inducible genes

MyD88 Dependent Pathway

MyD88 Independent Pathway

TRAM

TRIF
**Traumatic Injury Model**

- **Bilateral Femur Fracture**
- **Resuscitation prn (keep MAP > 60)**
- **Sacrifice**

- **6.0 hours**

- **Control animals**: anesthesia only
- **Sham**: unilateral femoral cannulation only
Decreased Systemic Inflammatory Response in TLR-4 Mutant Mice after Femur Fracture

(Levy RM et al, AJP 2006)
TLR-4 Mutant Mice Demonstrate Muted Hepatic Injury and Inflammatory Response After Femur Fracture

Liver Injury

EMSA for NF-κB Activity

(Levy RM et al, AJP 2006)
Two different routes for extracellular HMGB1

Activated Cells

Passive Release

Hyperacetylation

Necrosis

Apoptosis (HMGB1 sequestered)

Packaged into vesicles

Receptors:
- RAGE
- TLR4
- TLR2

Hyperacetylation Packaged into vesicles

inflammation
proliferation
migration

(Lotze and Tracey, Nature Rev Immunol 2005)
Traumatic Injury Model

- Bilateral Femur Fracture
- Resuscitation prn (keep MAP > 60)
- Sacrifice

- Control animals: anesthesia only
- Sham: unilateral femoral cannulation only

α HMGB1 or nonspecific IgG i.p. post Fx
Anti-HMGB1 Reduces Systemic Inflammation after Femur Fracture

**IL-6**

- Sham IgG
- Sham HMGB-1
- Fx IgG
- Fx HMGB-1

**IL-10**

- Sham IgG
- Sham HMGB-1
- Fx IgG
- Fx HMGB-1
Clinical Observation

Infection

PAMPs:
- LPS
- LTA
- Microbial DNA/RNA

DAMPs:
- HMGB1
- HSP
- Hyluronan

Pattern Recognition Receptors (TLR-4)

Activation of Innate Immune System

Systemic Inflammatory Response

Injury