William Coley

Coley’s Adjuvant
Cancer Syndrome

- Exposure to smoke
- Cough
- Hemoptysis
- Weight loss
- Mass
Diabetes Syndrome

- Thirst
- Polyuria
- Weight loss
- Blurred vision
- Tingling in the hands or feet

Banting and Best
Bacterial Infection Syndrome

- Fever
- Tachycardia
- Tachypnea
- Leukocytosis
- Suspected organ infection

Alexander Fleming
"Passive immunization against tumor necrosis factor/cachectin protects mice from the lethal effects of endotoxin."

Beutler, Milsark, & Cerami
Science 229:869, 1985
A controlled clinical trial of high dose methylprednisolone in the treatment of severe sepsis and septic shock

Sepsis Syndrome
(Bone et al; 1987)

Suspected or proven infection, in association with:

• Tachycardia
• Tachypnea
• Hyper- or hypothermia
• Dysfunction of one or more organs
Sepsis Syndrome

- 24 year old man with penetrating injury to colon
- 86 year old woman with CHF and Enterococcal UTI
- 51 year old man with COPD exacerbation; *Candida* in sputum
### Cytokine Levels in Human Sepsis

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Median (pg/ml)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF</td>
<td>83</td>
<td>7 – 57,151</td>
</tr>
<tr>
<td>IL-6</td>
<td>965</td>
<td>8 – 1,553,435</td>
</tr>
<tr>
<td>IL-8</td>
<td>2130</td>
<td>16 – 651,338</td>
</tr>
</tbody>
</table>

- MONARCS, Unpublished
Effects of Neutralization of TNF with MAK 195F on 28 Day All-cause Mortality

Survival Function

Days

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28

(p=0.049)

SEGARD
Placebo

- Panacek, Crit Care Med 32:2173, 2004
Probability of Mortality by Baseline IL-6 Level

IL-6 Level (pg/ml)
Influence of Infectious Challenge on Response to Neutralization of TNFα

Neutralization of TLR4 in Sepsis

- Opal, JAMA 309:1154, 2013
Impact of TLR4 Inhibition on 28 Day Survival

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Eritoran</td>
<td>p.</td>
<td></td>
</tr>
<tr>
<td>Gram positive</td>
<td>24.7%</td>
<td>33.8%</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>(N=182)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram negative</td>
<td>22.3%</td>
<td>21.9%</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>(N=215)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Trastuzumab Increases Survival in Her2-positive Breast Cancer

PCS9 is a critical regulator of the innate immune response and septic shock outcome

Suspected or proven infection, in association with:

- Tachycardia
- Tachypnea
- Hyper- or hypothermia
- Dysfunction of one or more organs
Suspected or proven infection, in association with:

- Tachycardia
- Tachypnea
- Hyper- or hypothermia
- Dysfunction of one or more organs

OR ...
• Endotoxemia

• PCSK9 gain of function mutation
Conclusion

• Sepsis, like cancer, is a useful concept

• Emphasizing the role of host defenses in the pathogenesis of acute illness

• But like cancer, it is inadequate to guide adjuvant therapy

• Which must be guided by the specific biologic process targeted
We don’t need new definitions …

... Instead we need better methods of stratification to target specific biologically active treatments to those patients most likely to benefit.
Thank You!!