Presenter Disclosures: N. Meyer

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  - None
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Ware and Matthay *New Engl J Med* 2000; Gotts and Matthay *Crit Care Clin* 2011;
ICU as the Pharmaceutical Graveyard

Opal, Fisher et al. CCM 1997
Gap in Translation: Why?

> 40 years of research dedicated to understanding cellular mechanisms in ALI

**Heterogeneity:**
- Phenotypic
- Proteomic
- Genetic

NO SPECIFIC PHARMACOLOGIC THERAPY
GABRIEL Asthma Consortium
10,000 Cases/ 16,000 Controls
Heritability ~60%

Moffatt MF / GABRIEL consortium NEJM 2010
Trauma-Associated ALI

600 ALI, 2200 Controls
Underpowered;
Heritability = ??

p < 10E-7

Did not replicate

p < 10E-5

Replicated Genetic Variants Influencing ALI Susceptibility and Outcome

- SFTPB
- MYLK
- IL-6
- IL-10
- MBL2
- PBEF
- FAS
- ANGPT2
- IL1RN
- VEGFA
- ACE
- PAI-1
- SOD3
Targeting Endothelial Permeability: Maintain Adherens Junctions

Komarova Y, Malik AB. Annu Rev Physiol 2010;72:463
Vascular Endophenotype?

- Angiopoietins 1 and 2 compete to bind TIE2 receptor
- ANG1 phosphorylates TIE2, quiescent endothelium
  - ANG2 binds, rarely phosphorylates TIE2
Targeting ANG1 / ANG2: Animal evidence

- **Recombinant ANG1**
  - CLP: improved survival time, decreased lung permeability
  - VILI: altered signaling but not permeability

- **PEG-TIE2 agonist (VT):**
  - Improved mortality
  - Decreased permeability
  - CLP and LPS IV
  - Effective if given post-insult

Hegeman *PLoS One; David Cyokine; David AJP Lung*
**ANGPT2 Phenotype?**

- *ANGPT2* SNP is associated with both trauma-associated ALI and a higher proportion of variant isoform
  - OR for ALI ranged 1.20 – 2.0
  - SNP associates with altered plasma isoform ratio

- **rs1868554T**
  - Linked loci

- **Increased full length ANGPT2**

- **Altered Vascular Permeability?**

- ↑ALI Susceptibility

Anti-ANG2 therapy (? PEG-TIE2 agonist) available soon

Meyer *AJRCCM* 2011
Limit anti-ANG2 Trial to Those with Molecular ANG2 Risk?

**GENE**
- Risk Genotype Defines ~40% Population

**PROTEIN**
- Elevated plasma ANG2
- *Specific ANG2 Isoform?*
- ANG2 : ANG1 Ratio
- ANG2 : VEGF Ratio
**IL1RN Phenotype?**

<table>
<thead>
<tr>
<th>SNP</th>
<th>Stage I: Trauma Cohort OR (95% CI)</th>
<th>Stage II: Trauma Case-Ctrl OR (95% CI)</th>
<th>Stage III: Mixed ICU Cohort OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs315952 syn-coding</td>
<td>0.37 (0.22 – 0.95) p = 0.00019</td>
<td>0.67 (0.52 – 0.88) p = 0.0023</td>
<td>0.83 (0.71 – 0.96) p = 0.015</td>
</tr>
</tbody>
</table>

- rs315952 associates with decreased ALI risk
- Associates with higher protein, mRNA IL1RA level

Meyer ATS abstract 2010
Several large studies (>2500 subjects total) examined rhIL1RA in sepsis

Signal for benefit (mortality) for the sickest patients, though never statistically significant

 Might variation in \( IL1RN \) (or \( IL1b \) ...) influence response to exogenous IL1RA?

JAMA 1994; CCM 1997
IL1RN Phenotype?

- Consistent direction of effect for reduced mortality
  - Unable to prove a reduction despite > 2000 subjects
- Would the results be different if rs315952C subjects were removed?
Surfactant Protein B Phenotype?

Effect of Exogenous Surfactant (Calfactant) in Pediatric Acute Lung Injury
A Randomized Controlled Trial

• \textit{SFTP}{B} variant +1580 associated with need for mechanical ventilation in pneumonia
• VNTR associated with death in ARDS
• Function of these variants unknown
• Test exogenous repletion in \textit{\Delta SFTP}{B} adults?

Wilson \textit{JAMA} 2005; Dahmer \textit{Crit Care Med} 2011; Quasney \textit{Crit Care Med} 2004
Beyond DNA: mRNA

- Gene expression-based subclassification
- Identified sepsis group with poor prognosis
- Glucocorticoid receptor signaling significantly dysregulated
- Role for testing therapy based on GE class?

Wong BMC Medicine 2009; Wong Crit Care Med 2011
Implications

• Bayesian genomic approach can identify risk variants with therapeutic potential
• Multicenter collaborations vital to effectively evaluate genetic contributions to ALI
• Genotype may be an important consideration in designing ALI pharmacologic trials
• Genotype – stratified clinical trials are a realistic possibility
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K23 HL102258
K12 HL090021
PO1 HL079063
RO1 HL081619
R01 HL060710
R01 GM066946
R01 HL081332
K23 HL090833
K08 GM085687

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IL1RN Genotype:
rs315952C

Risk for ALI ↓

IL1RA / IL1β ↑/↓

Non-genetic Factors:
- Obesity / BMI
- Inflammatory stimulus
- WBC count

Selection:
- Starvation
- Infection
- Hemorrhage

Low Risk Group: poor target for recombinant IL1RA therapy