ARDS – Do Molecules Matter?

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Conflicts of Interest

No financial conflict of interest with the subject matter of this talk
Research Support

- Dr Geoffrey Barker Chair in Critical Care Research
- 2 Operating Grants - CIHR
Molecules

4 Short Stories
Molecules - 1

Carbon Dioxide
Hypercapnic acidosis in ventilator-induced lung injury

In Vivo Mice
How does this work?
Hypercapnia attenuates ventilator-induced lung injury via a disintegrin and metalloprotease-17

Gail Otulakowski¹, Doreen Engelberts¹, Galina A. Gusarova³, Jahar Bhattacharya³, Martin Post¹ and Brian P. Kavanagh¹,²

Sheddase in Action

<table>
<thead>
<tr>
<th>Normocapnia</th>
<th>Calcein</th>
<th>TNFR1 BL 0min</th>
<th>TNFR1 BL 60min</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Stretch</td>
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Normocapnia

Hypercapnia

+Stretch

J Physiol 2014
Hypercapnia attenuates ventilator-induced lung injury via a disintegrin and metalloprotease-17

Gail Otulakowski¹, Doreen Engelberts¹, Galina A. Gusarova³, Jahar Bhattacharya³, Martin Post¹ and Brian P. Kavanagh¹,²

**Sheddase in Action**

![Graph showing Alveolar TNFR1 (grey levels) vs Time (min)]

**STRETCH**

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J Physiol 2014
Blocking Shedase – *in vivo*

Protein Leak

![Graph showing protein leak comparison between Vehicle and TAPI 2 treated groups.](https://example.com/graph.png)

J Physiol 2014
$CO_2$ – Patients?
Hypercapnic acidosis and mortality in acute lung injury

David A. Kregenow, MD; Gordon D. Rubenfeld, MD; Leonard D. Hudson, MD; Erik R. Swenson, MD

Adjusted Odds Ratio: Resp. Acidosis - Present vs. Absent

![Graph showing Adjusted Odds Ratio for Resp. Acidosis]
CO$_2$

- *May* have a role in clinical ARDS

- May be a tool to uncover ‘*blockable*’ injury pathways
Molecules - 2

Gene Activation
Early Changes in Lung Gene Expression due to High Tidal Volume

Ian B. Copland, Brian P. Kavanagh, Doreen Engelberts, Colin McGerlie, Jaques Belik, and Martin Post
Early growth response factor-1 in acute lung injury

Nicola Ngiam, Martin Post, and Brian P. Kavanagh

High $V_T$ → Signaling → $\uparrow$ EGR1 → EGR1-Target Gene

($Nur77, HSP70, PGE_2 Synthase$)
What happens if we delete the Egr1 gene?

**Respiratory Compliance**

![Graph showing changes in compliance over time](graph)

- **Egr1<sup>++/+</sup>**
- Compliance (kPa/ml)
- Baseline: 1.00 ± 0.10
- 1 hour: 0.80 ± 0.10
- 2 hours: 0.60 ± 0.10
- 3 hours: 0.40 ± 0.10

Ngiam et al, AJRCCM 2010
Early Growth Response-1 Worsens Ventilator-induced Lung Injury by Up-Regulating Prostanoid Synthesis

Nicola Ngiam¹*, Vanya Peltekova¹*, Doreen Engelberts¹*, Gail Otulakowski¹, Martin Post¹, and Brian P. Kavanagh²,³

¹Physiology and Experimental Medicine, ²Department of Critical Care Medicine, and ³Department of Anesthesia, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

Compliance Impairment

Delta Static compliance (baseline - final)

Control: No Blocker
At least some genes are over (or under) expressed in lung injury:

- Inhibit injurious gene products
- ‘Knockdown’ injurious mRNA
- Augment protective gene products
Molecules - 3

Circulating Mediators
Lung-derived soluble mediators are pathogenic in ventilator-induced lung injury

Thomas Jaecklin,1 Doreen Engelberts,1 Gail Otulakowski,1 Hugh O’Brodovich,3 Martin Post,1 and Brian P. Kavanagh1,2
Lung-derived soluble mediators are pathogenic in ventilator-induced lung injury

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Confirmation by ‘Transplantation’

- Ventilate with High $V_T$ or Low $V_T$
- Collect, store the perfusate
- Use it *next day* – Low $V_T$ ventilation
Lung-derived soluble mediators are pathogenic in ventilator-induced lung injury

Thomas Jaecklin,¹ Doreen Engelberts,¹ Gail Otulakowski,¹ Hugh O’Brodovich,³ Martin Post,¹ and Brian P. Kavanagh¹,²

![Graph showing BAL protein concentration in Low V_T Recipients with different perfusate sources: High V_T Donor, Fresh Perfusate, and Low V_T Donor. The graph indicates a significant difference in protein concentration between the Low V_T Recipients and the other groups, marked as ns (not significant).]
Circulating Molecules can Cause *and* worsen VILI

Characterize ... *(tried, failed)*

- *Inhibit*
- *Adsorb*
- *Filter*
Molecules - 4

Neutrophil NETs
Citrullinated Histones
(Key element of NETs)

NETs ‘Associated’ with maximum injury.

Anesthesiology 2015
Mechanical Ventilation Induces Neutrophil Extracellular Trap Formation

Citrullinated Histone co-localized with DNA in lung injury ... NET formation – no impact on injury
NETS occur in VILI but do not contribute to the injury
Conclusions ...

$\text{CO}_2$ - treat or uncover mechanisms

Gene Products - Inhibit/Augment

Remove/Inhibit Circulating Mediators

Role of NETs unclear

_Treat the Lungs Gently - Molecules may matter_
Thank You
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