Influenza Therapeutics

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October 29, 2018
Influenza Antivirals as of September 2018

**Adamantanes:**
- M2 blockers
  - Rimantadine
  - Amantadine

**Neuraminidase inhibitors**
- Oseltamivir
- Zanamivir
- Peramivir

Adamantanes: M2 blockers

- Rimantadine
- Amantadine

Neuraminidase inhibitors

- Oseltamivir
- Zanamivir
- Peramivir

Stiver 2003 CMAJ 168:49
Current Portfolio Focused on Direct-Acting Antivirals

Stem-binding Monoclonal Antibodies

Endonuclease Inhibitors

HA

VIS410

Pimodivir

Baloxavir

Adapted from Ruigrok. 2010. Current Opinion in Structural Biology. 20:104
Influenza Therapeutic Developments: Baloxavir

Infectious virus shedding was shorter in the baloxavir treated group
• 72 hours less shedding compared to placebo
• 24 hours less shedding compared to oseltamivir

Baloxavir significantly improves symptom alleviation compared to placebo

But not oseltamivir, why?

Hayden. 2018 NEJM 379:913
Less Emphasis on Hospitalized Studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Seasons</th>
<th>Clinical Sites</th>
<th>Numbers Enrolled</th>
<th>Patients/Site/Season</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peramivir</td>
<td>3 NH, 3 SH</td>
<td>196</td>
<td>405</td>
<td>0.69</td>
</tr>
<tr>
<td>IV zanamivir</td>
<td>5 NH, 4 SH</td>
<td>110</td>
<td>626</td>
<td>1.26</td>
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<tr>
<td>MHAA4549A</td>
<td>3 NH, 2 SH</td>
<td>172</td>
<td>127</td>
<td>0.30</td>
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<tr>
<td>IRC002 Immune Plasma</td>
<td>5 NH</td>
<td>35</td>
<td>98</td>
<td>0.56</td>
</tr>
</tbody>
</table>

- Inefficient
- Take a long time to enroll
- Expensive
- Global sites have variable standards of clinical care
- No clinical endpoint for this population
- Mostly unsuccessful

New Focus: Immune Modulators for Severe Influenza Infections

Immune compromised patients can shed virus for 7-8 weeks without excess morbidity

Biomarkers of inflammation associated with poor outcomes in influenza infected patients

Lehners. 2016 PLoS ONE. 11:e0148258

Where are the Immune Modulator Submissions?

IL-33 increases with influenza infection

Treatment with macrolides reduces symptom scores in hospitalized patients

Neutropenic mice are protected from death

AnaptysBio
Anti-IL-33 in phase 2

REGENERON
Anti-IL-33 in phase 1

IL-33 (pg/ml)

0 200 400 600 800
Control Infected

**

IL-33 increases with influenza infection


Navarixin, selective CXCR2 antagonist, in phase 2 for COPD


Treatment with macrolides reduces symptom scores in hospitalized patients

Lee. 2017. Antiviral Res. 144:48

Azithromycin

Danirixin, selective CXCR2 antagonist, in phase 2 for COPD

Navarixin, CXCR2 antagonist, in phase 2 for COPD

Azithromycin
Requirements for BARDA BAA Submission have not Changed

1. Must have an open US IND for influenza
2. Phase 1 data must be available for review
3. Drug must be safe!
4. Demonstrated activity against seasonal & potential pandemic influenza

If you need help conducting these early development studies, please contact Amy Krafft at NIAID, kraffta@niaid.nih.gov or 240-627-3295
New Influenza Therapeutics Plan

Current strategy
new mechanisms
of action

Strategies
we are
interested in

Immune modulators

One of many potential
pathways to target

Pimodivir
Baloxavir
Monoclonal
antibodies

Galani 2017 Immunity. 46(5):875
How to contact BARDA

- medicalcountermeasures.gov
  Portal to BARDA: Register to request a TechWatch meeting!

- www.fbo.gov/ (“FedBizOpps”)
  Official announcements and info for all government contract solicitations

- https://www.phe.gov/about/BARDA/Pages/default.aspx
  Program description, information, news, announcements

- www.drive.hhs.gov
  DRIVE questions

- https://www.usajobs.gov
  Join the team!