Fasciola hepatica Vaccine Update

Grace Mulcahy
UCD School of Veterinary Medicine
ARE WE THERE YET !?!
Why Vaccines?

- Cattle and sheep of all ages
- Clinical and sub-clinical effects
- Immune compromise
- The drugs don’t work (sometimes)
Leg Brick vs Lego City

Virus vs. Helminth Parasite
Immunoregulation by Fluke

- Mice
- Cattle, Sheep

Salmonella? Clostridial Diseases?
IFN-\(\gamma\) response to (PPDB-PPDA)

M. bovis only
M. bovis and F. hepatica

Net Optical Density

Weeks post infection
The Challenge of Vaccination

- Protective responses
- Immune distortion
- Outcome
What Does a Fluke Vaccine Need to Do?

- Protect against natural challenge
- Prevent/reduce loss of productivity
- Block transmission
- Reduce need for drug treatment
- Prevent immunoregulation
Candidate /Experimental Vaccine Antigens – Recombinant

- Cathepsin L1 (Cathepsin L3)
- Cathepsin B
- Peroxiredoxin
- Leucine amino-peptidase
- Fatty-acid binding protein
- Glutathione-S-transferase
Leucine Amino-peptidase

- High levels of protection in sheep
- IgG1 and IgG2
- Relatively short-lived antibody responses

Maggioli et al., Vaccine 29: 8057-9063 2011
Recombinant Mutant CL1

Properties of FhCL1

- Acquire nutrients by breaking down proteins to peptides
- Degrades interstitial matrix proteins
- Involved in immuno evasion mechanism
- Suppress Th1 response
# FhCL1 in Previous Experiments

<table>
<thead>
<tr>
<th>Trial Research</th>
<th>Species</th>
<th>Antigen</th>
<th>Reduction fluke burden (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalton <em>et al.</em> 1996</td>
<td>Cattle</td>
<td>FhCL1, FhCL2, FhCL1+FHb, FhCL2+FHb</td>
<td>53.7, 72.4</td>
</tr>
<tr>
<td>Mulcahy <em>et al.</em> 1998</td>
<td>Cattle</td>
<td>FhCL2+FHb</td>
<td>72</td>
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<tr>
<td>Piacenza <em>et al.</em> 1999</td>
<td>Sheep</td>
<td>FhCL1, FhCL2, FhCL1+FhCL2</td>
<td>33, 60</td>
</tr>
<tr>
<td>Van Milligan <em>et al.</em> 2000</td>
<td>Rats</td>
<td>FhCL3 intra-peritoneally</td>
<td>92.6</td>
</tr>
<tr>
<td>Kofta <em>et al.</em> 2000</td>
<td>Rats</td>
<td>cDNA encoding Fh.Cysteine protease</td>
<td>74</td>
</tr>
<tr>
<td>Wedrychowicz <em>et al.</em> 2003</td>
<td>Calves Lambs</td>
<td>cDNA intranasally</td>
<td>54.2, 56.5</td>
</tr>
<tr>
<td>Golden <em>et al.</em> 2010</td>
<td>Cattle</td>
<td>rmFhCL1</td>
<td>48.2</td>
</tr>
</tbody>
</table>
## Small Scale Vaccine Field Trial – rFhCL1

<table>
<thead>
<tr>
<th>V1 - 6 weeks</th>
<th>Confirm absence of fluke infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>V1</td>
</tr>
<tr>
<td>+3 weeks</td>
<td>V2</td>
</tr>
<tr>
<td>+6 weeks</td>
<td>Onto fluke pasture together</td>
</tr>
<tr>
<td>+20 weeks</td>
<td>Slaughter &amp; count flukes in livers</td>
</tr>
</tbody>
</table>
Protection in low-challenge field trial

Golden et al. 2010.
Assays for Protective Antibodies - Avidity

**Chaotropic Assay**

\([\text{KSCN}]\) needed to reduce antigen-antibody binding by 50%

Golden *et al.*, 2010 *Vaccine* 28: 5551-5557
Control 12 weeks post-challenge

Vaccinated 12 weeks post-challenge
Macrophage Activation

![Graph showing arginase activity](image)

- **Control**
- **ISA 70VG**
- **ISA 206VG**

Arginase activity (milli-Units per $10^6$ cells)

- **Exposure**
- **4wpe**
- **12wpe**

Significance levels: *p < 0.05*, **p < 0.01**
University College Dublin – Ireland

Paravac
Large Scale Clinical Trial in Cattle

> 200 animals
Different age-groups

Vaccinated

Matched Controls

Followed for 2 years
And/or slaughtered as per commercial requirements
Experimental Plan

- Animals from three Irish farms where liver fluke is known to be present (all belong to Teagasc Institute)
Johnstown Castle– Quantitative ELISA Titration of IgG1 and IgG2 Responses
<table>
<thead>
<tr>
<th>No. of Pos Samples</th>
<th>Vaccinates</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative Egg Counts</td>
<td>99</td>
<td>187</td>
</tr>
<tr>
<td>No. of Pos Samples</td>
<td>32</td>
<td>42</td>
</tr>
</tbody>
</table>
Faecal Eggs – Frequency Distribution

![Graph showing the frequency distribution of faecal eggs across different ranges. The graph compares the vaccinated (Vax) and control groups. The x-axis represents the egg counts, ranging from 0 to 29, and the y-axis represents the frequency. The graph shows a peak in the 0-4 range for both groups, with a gradual decrease as the egg count increases. The vaccinated group has a higher frequency in the 0-4 range compared to the control group.]
Vaccines are a Realistic Goal

- Liver Fluke Systems Biology
- Liver Fluke Genetics
- Interactions of Drug treatment and vaccination
- Interactions of immunoregulation and vaccination

A Vaccine is more than an antigen or even an antigen cocktail
ARE WE THERE YET?
Thanks to.....

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