Lyme Disease: Prevention strategies

Apparently they’re better than the Cure . . .
Lyme Disease: Prevention strategies

- Target: Humans
  - Human vaccines
  - Tick avoidance
    - clearance of brush
    - clothing
    - repellents
    - daily tick checks
    - showering
  - Prophylactic antibiotics

1. Larva feeds on first host
2. Eggs hatch into spirochaete-free larvae
3. Replete larva drops to ground and moults to nymph
4. Nymph feeds on second host
5. Replete nymph drops to ground and moults to adult
6. Adult feeds on third host
7. Incidental or dead-end host
8. Erythema migrans

Notes:
- Red X marks steps that are not followed in the cycle.
Lyme Disease: Prevention strategies

- Target: Deer
Lyme Disease: Prevention strategies

- Target: Ticks
  - acaricidal spraying
  - Dammininx
  - 4-poster
Lyme Disease: Prevention strategies

- Target: Mice
  - kill all mice
  - antibiotic treatment to eradicate *B. burgdorferi* from mice and ticks
  - reservoir targeted vaccination
Lyme Disease: Prevention strategies

Reservoir targeted vaccination

- Field injection of OspA (Tsao et al)
- Decreased incidence of Bb carriage in ticks the following season
Prevention/Vaccine

Outer surface protein A (OspA)

- Outer membrane lipoprotein
- Plays a role in attachment of Bb to tick midgut
- Expressed by Bb in ticks and *in vitro* culture, but minimally in mammalian host
OspA Vaccination

- Prevents transmission from ticks to humans or mice
- Clears infection from infected ticks fed on vaccinated animals
- Prevents uptake of Bb by ticks from vaccinated infected animals

Lymerix, SmithKline Beecham
Lyme Disease: Vaccine Distribution

- Needs to be oral
  Feeding of recombinant OspA
  Advantage: less risk for toxicity
  Disadvantage: requires multiple doses

Viral vector delivery
  Advantage: more immunogenic
  Disadvantage: infectivity of vector
Field trial of recombinant *E. coli* expressing OspA

Vaccinia virus

- Infects wide range of cells
- Infects wide range of animals
- Can be delivered orally
- Natural booster/adjuvant activity
- No animal to animal transmission
- Already studied in environmental release
Rabies-Vaccinia vaccine

Rabies and Vaccinia

- Air dropped baits
- Targets raccoons and foxes
- Reduced incidence by 85-95%
- Incidental human infection rare (2 cases to date; >80 million doses distributed)
Bait Protection

Bb-infected *Peromyscus* mice vaccinated with VV-OspA or control vaccine

4 weeks to generate anti-OspA antibody

Feed larvae on infected, vaccinated mice

Determine Bb infection in fed larvae

<table>
<thead>
<tr>
<th></th>
<th># Fed larvae recovered</th>
<th># Larvae infected</th>
<th>% Larvae infected</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>VV-OspA</em></td>
<td>57</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>VV-vp37 control</em></td>
<td>53</td>
<td>38</td>
<td>71.6</td>
</tr>
</tbody>
</table>

P = 0.0001
Bait Protection

Uninfected *Peromyscus* mice vaccinated with VV-OspA or control vaccine

4 weeks to generate anti-OspA antibody

Challenged with Bb-infected nymphs

Determine Bb infection in mice

<table>
<thead>
<tr>
<th></th>
<th># mice vaccinated</th>
<th># Bb-infected mice post challenge</th>
<th>% mice infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>VV-OspA</td>
<td>10</td>
<td>1 *</td>
<td>10</td>
</tr>
<tr>
<td>VV-vp37 control</td>
<td>6</td>
<td>4</td>
<td>66.67</td>
</tr>
</tbody>
</table>

* Mouse did not develop an anti-OspA antibody response

P = 0.03
Challenges

• Will vaccine reactions in wild mice be similar to laboratory reared mice (e.g. will exposure to natural infections alter responses?)

• Will availability of natural diets, social behaviors or other variables change the performance of the vaccine?

• What will be the impact of the vaccine on non-target animals?

• Will the vaccine be efficacious if it does not protect other contributors to the wild reservoir (chipmunks, squirrels, birds)?
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Inherited Immunity vs Tick-Borne Disease

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white-footed deer mice

Mouse immune systems evolve new genes…

… encoding antibodies that flag the target for immune system attack

Each mouse must be independently vaccinated and evolve its own solution
vaccinate

white-footed deer mice

make antibodies

identify best binders

make mice with inherited immunity

sequence antibody-encoding genes

test immunity with infected ticks

most resistant
Born with immunity

*This works:* mice given genes encoding antibodies have been immunized vs HIV, malaria, hepatitis C, influenza

Genome

CRISPR/Cas9

Guide RNA

Antibodies (inherited immunity)

Balazs et al (2013) *Nat Biotech*
white-footed deer mice

make antibodies

identify best binders

make mice with inherited immunity

vaccinate

sequence antibody-encoding genes

test immunity with infected ticks

most resistant

most resistant

most resistant
Antibodies (inherited immunity)
For widespread immunity, release mice equal to the local wild population

This is feasible for small islands and possibly large ones
vaccinate

white-footed deer mice

make antibodies

identify best binders

make mice with inherited immunity

test immunity with infected ticks

sequence antibody-encoding genes

make mice with inherited immunity

most resistant

most resistant

volunteer field trials

gene drive
Genome

CRISPR/Cas9
+ Inherited immunity
+ Guide RNA
Guide Cas9 Genome

Inherited immunity +
Guide RNA

CRISPR/Cas9

Genome

Guide
CRISPR gene drive spreads inherited immunity to all mice
vaccinate

white-footed deer mice

make antibodies

identify best binders

make mice with inherited immunity

sequence antibody-encoding genes

test immunity with infected ticks

make mice with inherited immunity

test immunity with infected ticks

most resistant

volunteer field trials

All mice have inherited immunity
Eliminate reservoir; no disease
Inherited Immunity vs Tick-Borne Disease: Options

**Immunize vs Lyme bacterium *B. burgdorferi***
- No effect on other tick-borne diseases
- No effect on ticks

- anti-Lyme cisgenic
- anti-Lyme CRISPR control transgenic
- anti-Lyme CRISPR gene drive transgenic

**Immunize vs tick salivary proteins**
- Reduces all tick-borne diseases
- Reduces tick population

- anti-tick cisgenic
- anti-tick CRISPR control transgenic
- anti-tick CRISPR gene drive transgenic