LYMErix
Lyme Disease Vaccine (Recombinant OspA)

Theoretical Considerations of Treatment-resistant Lyme Arthritis

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Treatment-resistant Lyme arthritis

The hypothesis - ***Gross et al. (1998) Science 31, 281***

- **TRLA is an autoimmune disease triggered by natural infection**
- **This autoimmune disease may be the result of a cross-reactivity between OspA and hLFA-1**
- **HLA-DR4 individuals are at risk of developing TRLA after natural infection**

Treatment-resistant Lyme arthritis
- The Gross et al. hypothesis -

1. Upon infection, *B. burgdorferi* invades the joints of some individuals
2. At this site, the bacteria:
   - induce an inflammatory process
   - start expressing OspA
3. An immune response is initiated against OspA

   -> OspA specific T-cells are stimulated
4. One OspA epitope recognized in HLA-DR4 individuals, has sequence homologies with a human protein, LFA-1
5. As a consequence, when OspA has disappeared, the LFA-1 epitope could continue to stimulate OspA-primed T-cells
6. These stimulated T-cells would perpetuate the inflammatory process

Treatment-resistant Lyme arthritis
- Discussion -

- Limitations of the hypothesis
- Does it apply to vaccination with OspA?
- Preclinical experiments

Treatment-resistant Lyme arthritis - Limitations of the hypothesis -

- **Autoimmune nature of TRLA**
  - **The absence of *B. burgdorferi* in "TRLA" joint is still debated**
- **T-cell cross-reactivity and autoimmunity**
  - ***In vitro* cross-reactivity is not sufficient to induce an autoimmune process** (**Hemmer et al. 1999,** *Nat.Med.* 5:1375-82; **Maier et al. 2000**, *Eur J Immunol* 30:448-57)
- **Identity of the auto-antigen**
  - **TRLA is observed in one (few) joint(s), while hLFA-1 is present on cells throughout the body**

Treatment-resistant Lyme arthritis
- Does the hypothesis apply to vaccination with OspA? -

Even if the *Gross et al.* hypothesis is confirmed, it does not apply to vaccination

- **The requirements for the development of TRLA are:**
  - **Presence of OspA in the joint**

    Borrelia expresses OspA when present in the joint
  - **Presence of "inflammatory milieu" in the joint**

    Borrelia induces inflammation in the joint
- **Theoretically, these requirements are not met upon vaccination.**
  - **This is supported by preclinical experiments**

Treatment-resistant Lyme arthritis
- Mice experiments - preliminary results -

- **C3H mice are susceptible to arthritis development upon infection with *B. burgdorferi***

  At day 28 post inoculation, clinical arthritis (joint swelling) is observed

- **Immunization of C3H mice with OspA does not induce arthritis**

  At day 28 post vaccination:
  - **no joint swelling observed**
  - **no inflammation detected in or around the joint**
  - **no OspA detected in or around the joint**

- **Conclusion (preliminary results):**
  Immunization with OspA does not create the milieu required for the development of the hypothetical autoimmune TRLA

Treatment-resistant Lyme arthritis
- Conclusion -

On the basis of

- The theoretical analysis of the TRLA concept,
- Preclinical experiments,

There is no evidence that vaccination with OspA induces the development of treatment-resistant Lyme arthritis.

These observations have been reviewed and conclusions agreed upon by a panel of independent experts in autoimmunity.

Further, since 1998, no new data have been published to further confirm the autoimmune TRLA hypothesis.