Lyme disease : from LYMErix to a European vaccine

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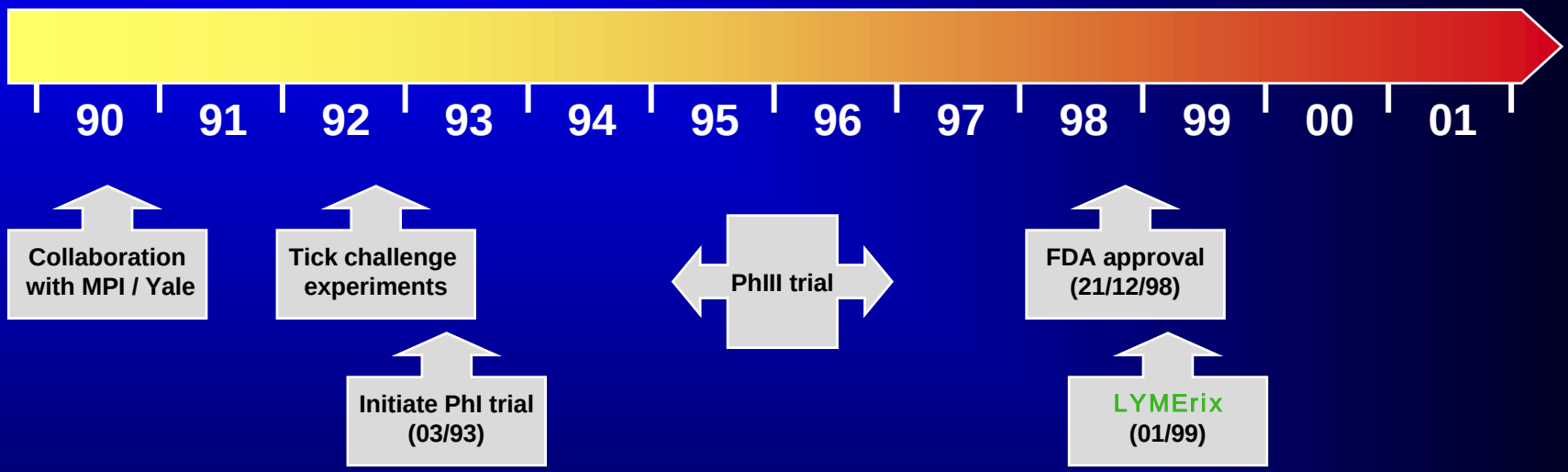
Presentation overview

- **From LYMErix...**
  - Rationale for OspA-based vaccine
  - Mechanism of protection
  - LYMErix

- **... to a European vaccine**
  - Borrelia in Europe
  - Lyme Europe vaccine composition
  - preclinical data
  - clinical data

From LYMErix...

LYMErix development: timeline



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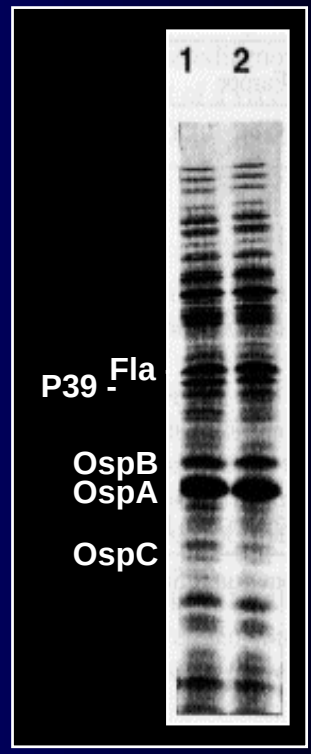
OspA: Outer Surface Protein A

- Major protein of
  B. burgdorferi sensu lato
- Lipoprotein
- Surface exposed
- Present on the bacteria within the tick



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OspA-based vaccine: initial observations

- *scid* mice are passively protected against infection and disease by poly- and monoclonal anti-OspA antibodies.
  Schaible et al. (1990) Proc Natl Acad Sci USA 87:3768

- Active immunization with OspA protects C3H/HeJ mice against infection and disease.
  Fikrig et al. (1990) Science 250:553

Protection in mice

Vaccine	Seroconversion to P39 (positive/ examined)	Culture (positive/ examined)	Infected ticks after challenge (positive/ examined (%)	Average no. of spirochetes within infected ticks
-	**5/8**	**4/10**	**8/22 (37)**	**300 - 1000**
OspA	**0/10**	**0/10**	**0/14 (0)**	**0**

In collaboration with Yale U./Harvard U.

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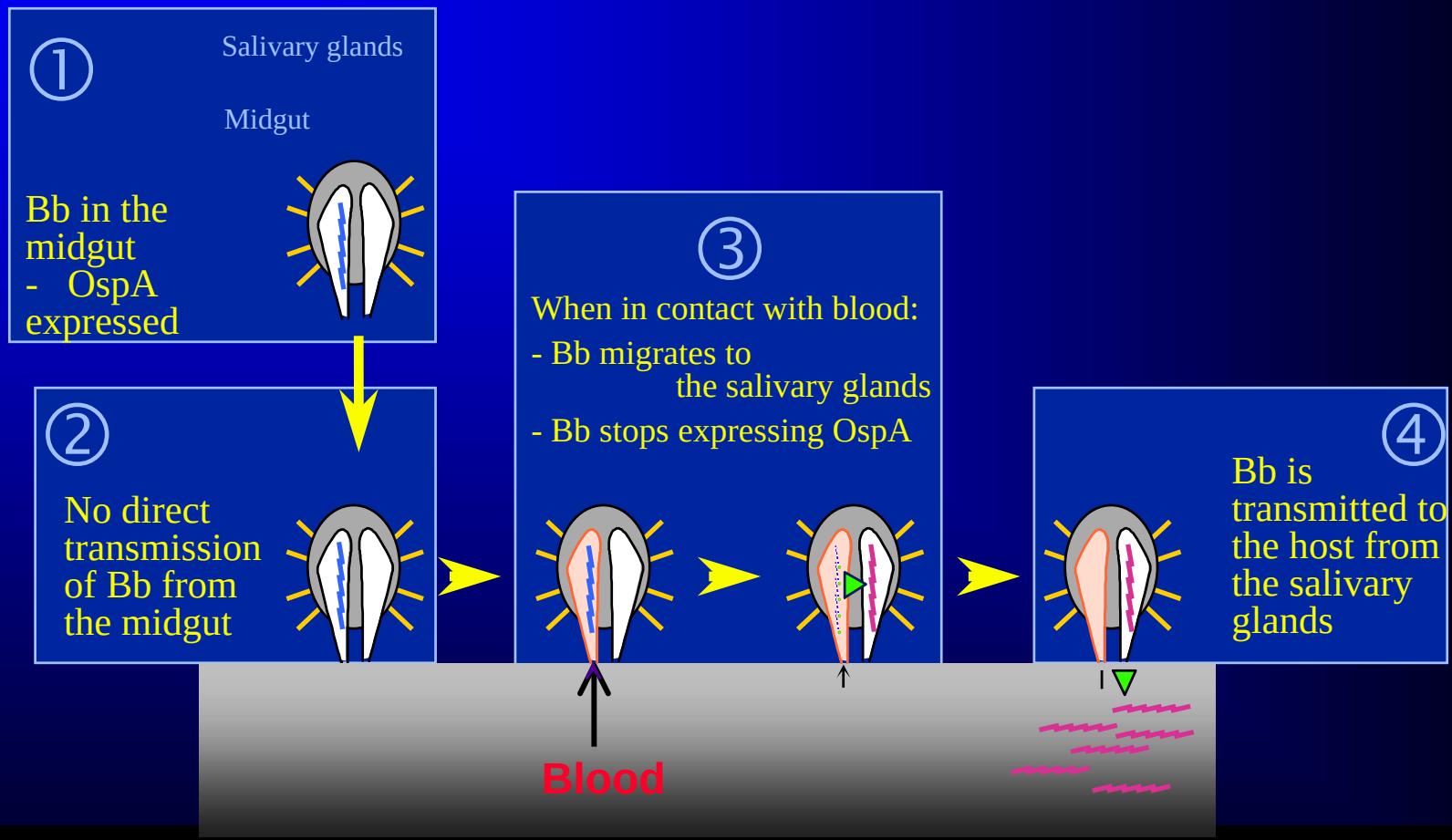
Borrelia transmission



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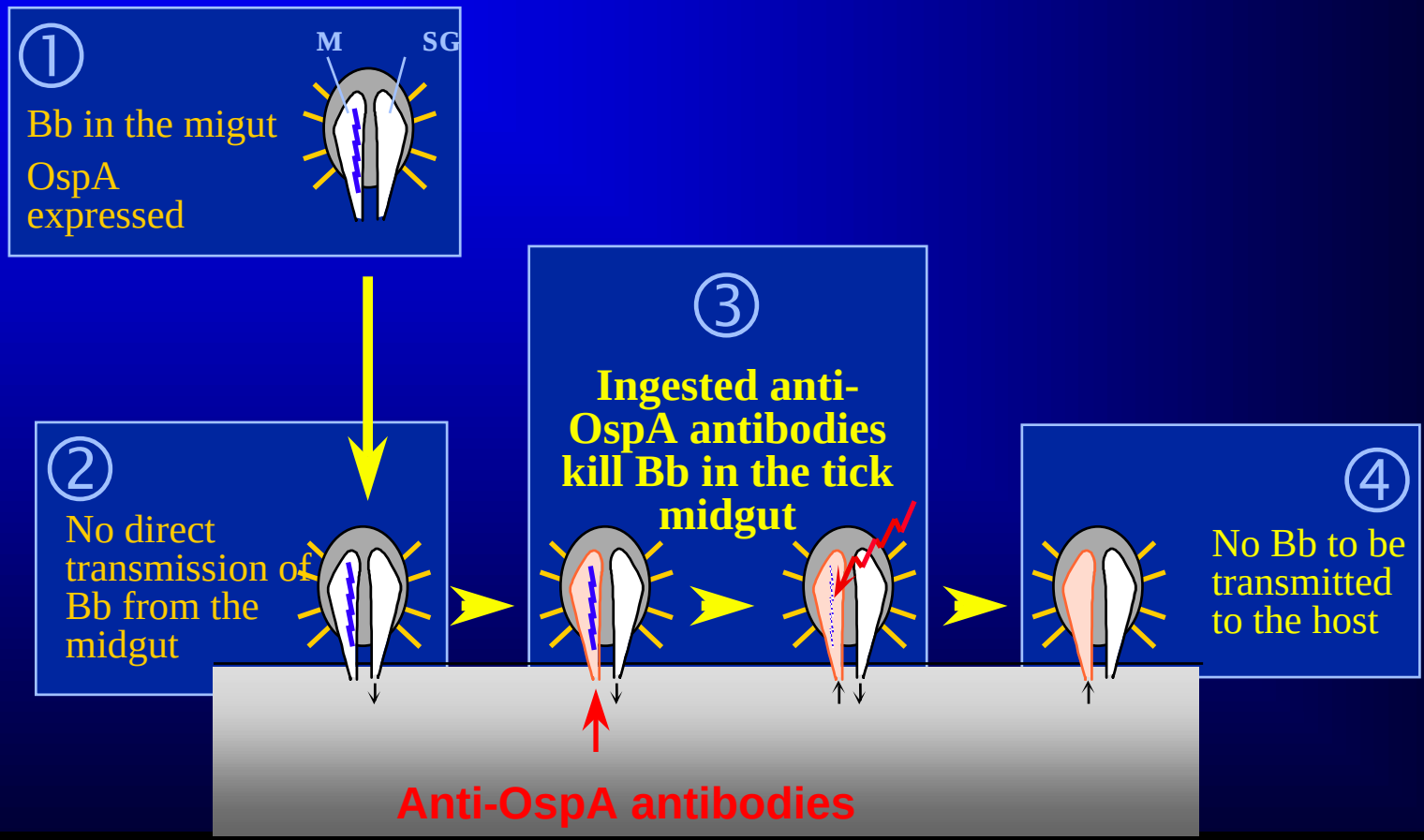
Proposed mode of action of OspA-based vaccine



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Mechanism of protection

- Borrelia is killed within the tick before its transmission.
- Both complement-dependent and -independent, antibody-mediated killing are involved in bacterial killing.
- The overall protective capacity of an immune serum is determined by serum bactericidal antibodies (SBA).
- Protection could be mediated by other mechanisms
  - Interference with OspA function

LYMErix®

- Antigen = 30 µg of OspA adsorbed on Alum
- Injections at 0, 1, 12 Mo
- Efficacy trial:
  - safety/reactogenicity OK
  - 78 % efficacy against disease
  - 100 % efficacy against asymptomatic infection
- Protects against *Borrelia burgdorferi* infection
- Launched in USA in January 1999
- *Discontinued in February 2002 because of poor sales…*

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Auto-immune arthritis?

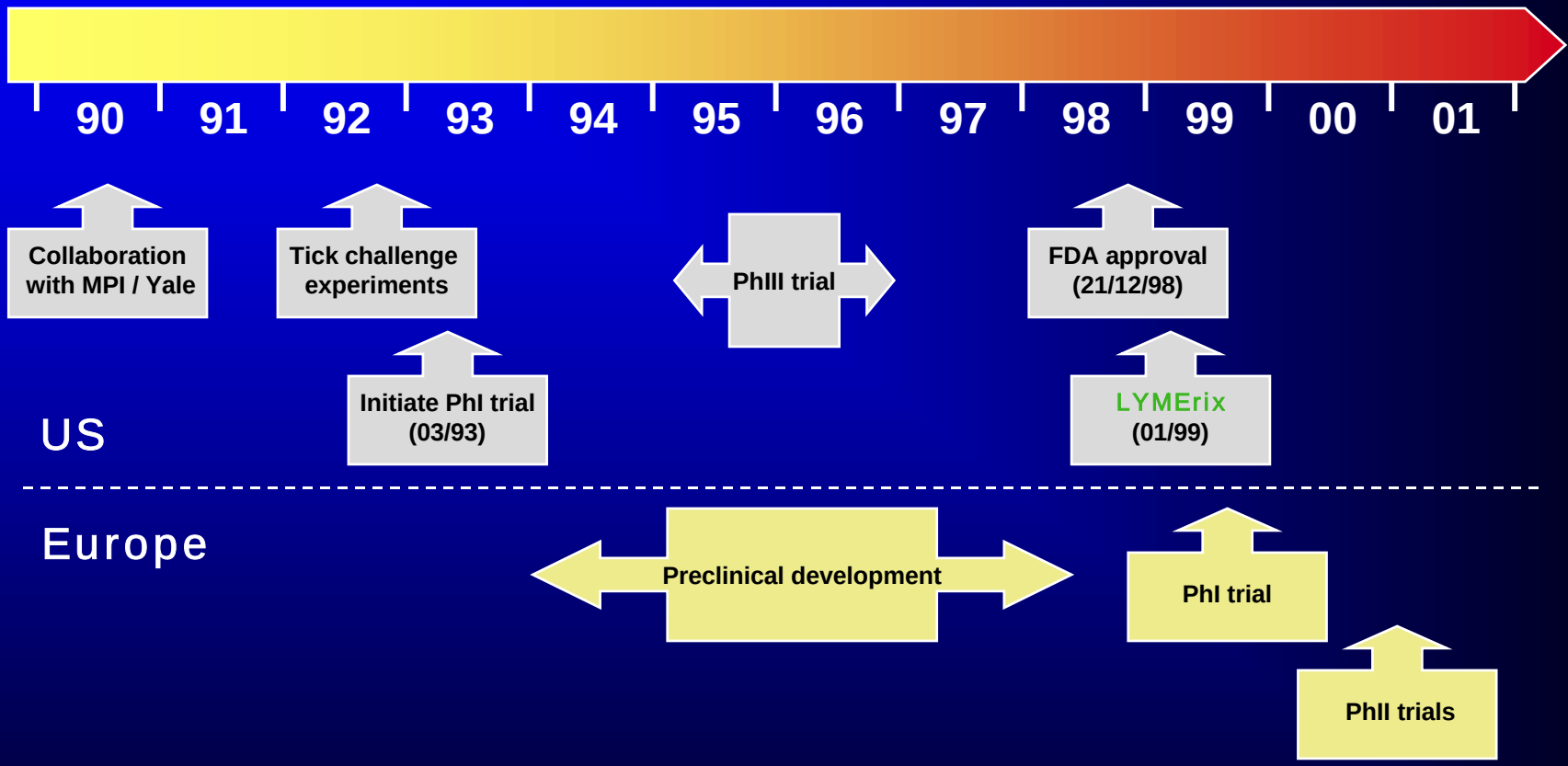
- In the hypothesis of Gross et al. (*Science* 31; 703 (1998)), OspA-induced autoimmune arthritis would be triggered after infection with *B. burgdorferi*.

  BUT

  - Molecular mimicry and T-cell cross-reactivity are not enough to explain an autoimmune reaction.
  - The requirements to induce an autoimmune disease, as described by Gross et al., are not present after vaccination.

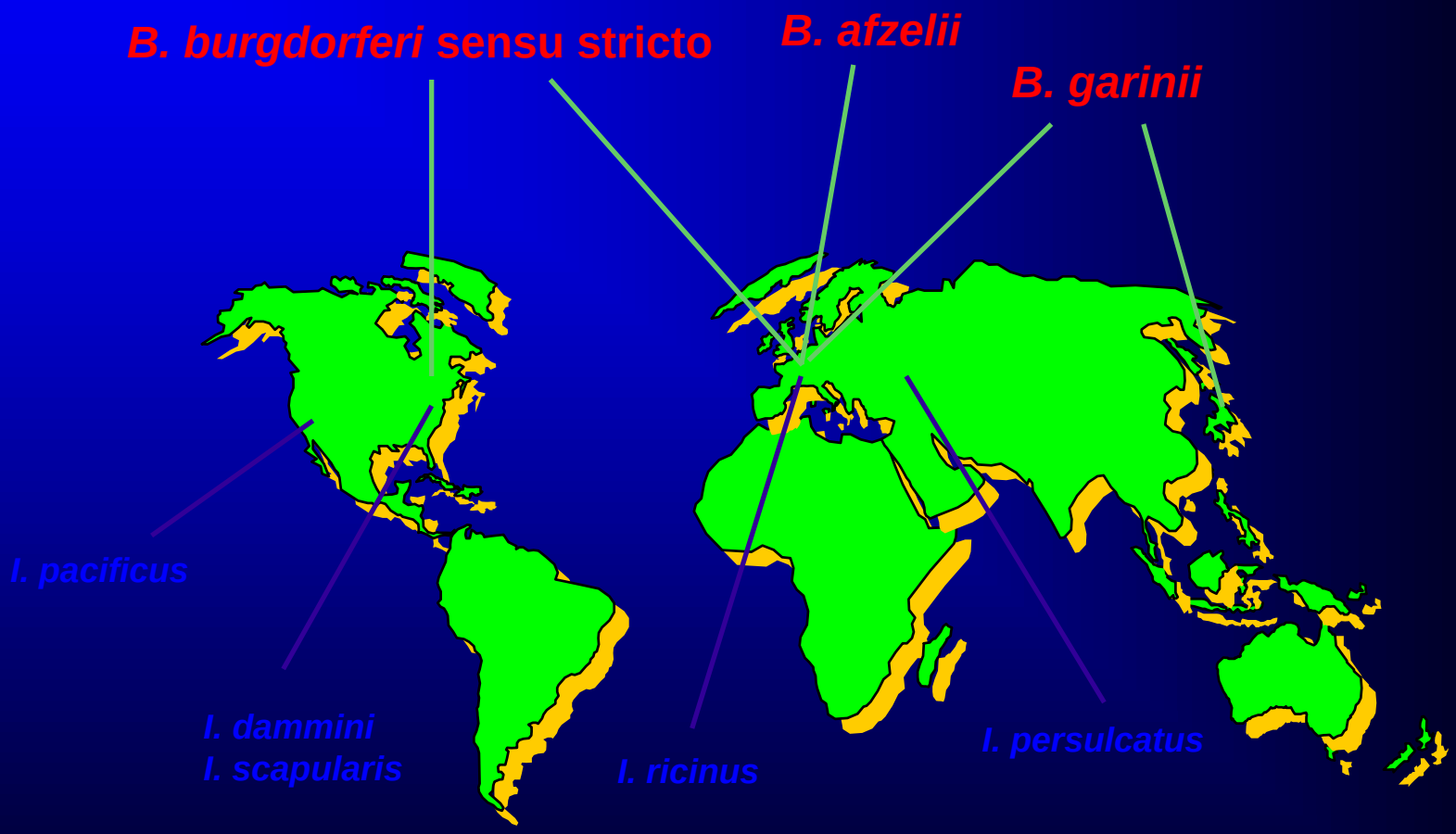
- With LYMErix, there is no clinical evidence of vaccine-induced arthritis.
  - Efficacy trial Lyme 008
  - Post-marketing surveillance

Lyme vaccine development: timeline



... to a European vaccine

Borrelia variability and distribution



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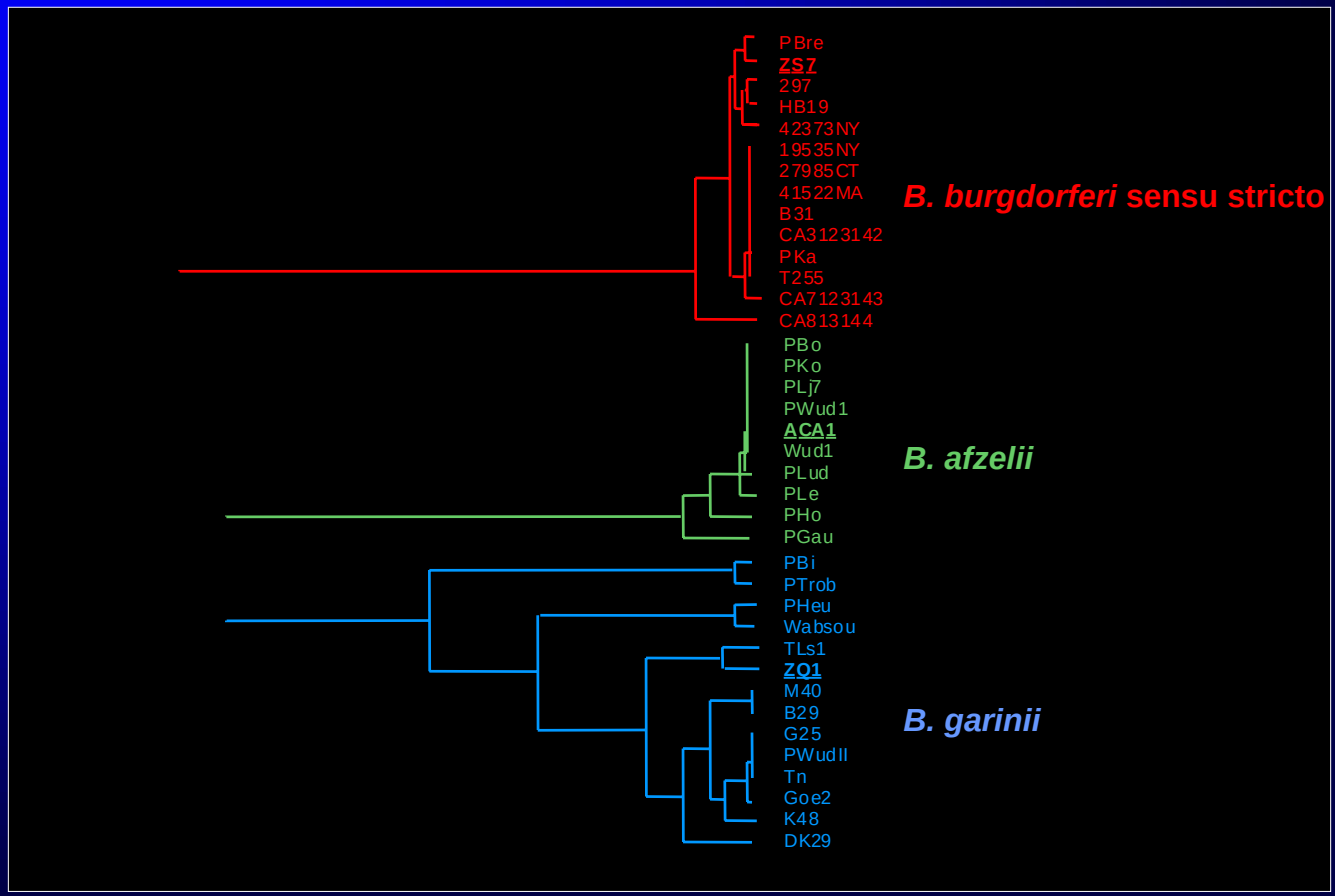
Borrelia burgdorferi sensu lato

- Three species isolated from humans:
  - *B. burgdorferi* sensu stricto, *B. garinii*, *B. afzelii*.
- Other species isolated from mammals, birds, ticks with occasional detection in humans:
  - *B. valesiana, B. andersonii, B. lusitaniae, …*

OspA variability within *Bbss*



Proposed composition of European vaccine

- $OspA_{ZS7}$ - *B. burgdorferi* sensu stricto (LYMErix)
- $OspA_{ZQ1}$ - *B. garinii*
- $OspA_{Aca1}$ - *B. afzelii*

3 x 30 µg, adsorbed on Alum

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Vaccine composition

- Advantages:
  - Covers all three Borrelia pathogenic species
  - Similar to LYMErix
    - concept
    - process

- Questions:
  - Covers all three Borrelia pathogenic species?
  - Safety of high dose of OspA (90 µg)?

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Lyme Europe vaccine: preclinical data

Questions

- Does the trivalent vaccine cover all serotypes of *B. burgdorferi* sensu lato?
- Coverage of the trivalent vaccine across Europe?

Tools

- Tick challenges
- Bactericidal antibodies

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Trivalent vaccine efficacy in mice (1)

- Comparison:
  1 µg $OspA_{ZS7}$
  vs
  0.3 µg $OspA_{ZS7}$ + 0.3 µg $OspA_{ZQ1}$ + 0.3 µg $OspA_{Aca1}$
- Procedure:
  - 3 immunizations (3 weeks interval)
  - Challenge (4 weeks post III) - ticks from Neuchatel area
  - Follow-up infection:
    - culture from skin biopsies (4, 10 weeks post challenge)
    - seroconversion
    - xénodiagnosis

Trivalent vaccine efficacy in mice (2)

Groups /mice	*Infected /tested*[1]	*phenotype*	*Phenotype (biopsy)*	*xeno 1*	*xeno 2*
Placebo					
1	4/4	Ba/Ba/Ba/Ba	Ba	7/7	nd
2	0/4	-	Ba	7/7	nd
3	2/8	Ba/Ba	Ba	6/7	nd
4	1/4	Ba	Ba	7/7	nd
5	0/5	-	Ba	7/7	nd
Mono					
1	1/4	VS116*	-	1/7	0/14
2	1/7	Ba	Ba	6/7	nd
3	0/4	-	-	0/7	0/14
4	2/7	Bg/Bg	Bg	1/7	2/14
5	1/11	nc	-	1/7	0/5
Tri					
1	0/5	-	-	0/7	0/14
2	0/6	-	-	0/7	0/14
3	0/9	-	-	0/7	0/14
4	0/3	-	-	0/7	0/14
5	0/5	-	-	0/7	0/14

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Trivalent vaccine efficacy
Geographic coverage

- Protection of (60) 75-100 % against challenges with ticks collected in:
  - Germany (Bavaria, Berlin, Black Forest)
  - Sweden
  - Finland
  - Switzerland
  - Austria
  - France
  - Belgium

Lyme Europe vaccine: clinical data

- Safety of the increased dosage of OspA - 90 vs 30 µg
- Immunogenicity - Interference?

EULY-002

3 groups	Group	# subjects
• 3 x 30µg candidate vaccine	1	300
• 3 x 20µg vaccine	2	100
• Lymerix	3	100

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EULY-002: Immune response and persistence

Vaccine	Timepoint	N	GMT	N	GMT
		IgG anti-Ospa Bb sensu stricto (EL.U/ml)		IgG anti-Ospa Bb sensu lato (EL.U/ml)	
EULY	PRE	300	10.0	298	10.3
	PII (month 2)	296	2130.2	297	4795.3
	PIII (month 3)	297	4297.6	297	9954.9
	PIII (month 6)	296	1505.0	297	3064.9
	PIII (month 9)	294	751.9	294	1514.3
LYMERIX	PRE	100	10.0	100	10.3
	PII (month 2)	98	1227.1	100	1131.0
	PIII (month 3)	99	3509.3	99	3749.3
	PIII (month 6)	99	1100.1	99	986.8
	PIII (month 9)	99	544.8	99	470.8

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European Lyme vaccine development summary

- Preclinical
  - Overall, protective immunity has been demonstrated against 6 of the 7 serotypes of pathogenic Borrelia.
  - Protection demonstrated against isolates from various countries
- Clinical
  - 90 µg candidate vaccine is safe and well tolerated
  - All three OspA are equally immunogenic
  - No immune interference between the three OspA

--> Next step: efficacy trial

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Thanks to...

- The members of the LYMErix and Lyme Europe project teams at GSK Bio

- Our collaborators at:
  - U. Neuchatel
  - MPI - Freiburg
  - Yale U.
  - Tulane U.
  - Berlin U.
  - CDC
  - NIH
  - Munich U.
  - ULB
  - UCL

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