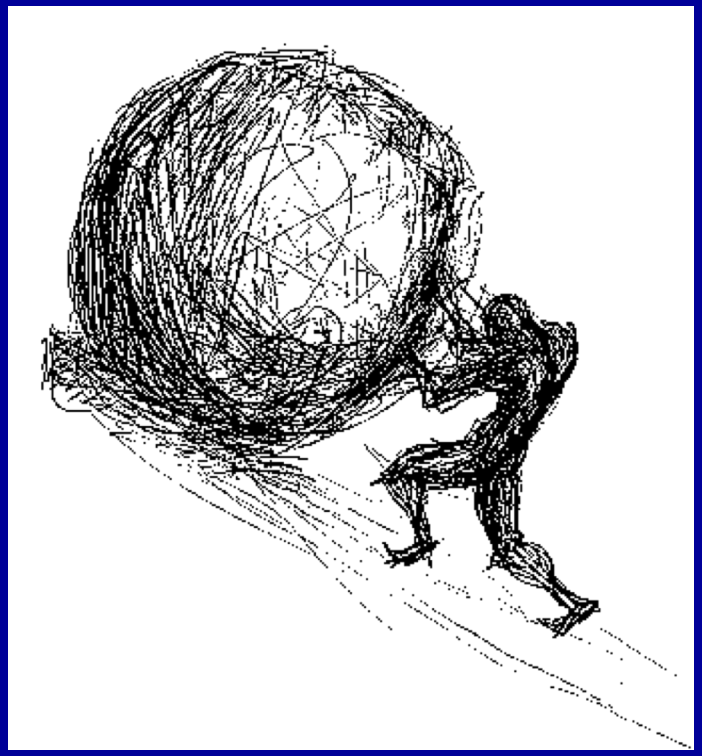
Anti-Staphylococcal Vaccine: Hope or Delusion?



International Society for Cardiovascular Infectious Diseases
Lausanne, Switzerland
June 4, 2019

Disclosures

Nature of Relevant Financial Relationship	Commercial Interest
Grant or research support	Allergan, Pfizer, NIH, MedImmune, Cubist/Merck; Karius; Contrafect; Genentech NIH STTR/SBIR grants pending: Affinergy; Locus, Medical Surface, Inc.
Paid consultant	Achaogen, Astellas, Arsanis; Affinergy; Basilea; Bayer; Cerexa, Contrafect; Cubist; Debiopharm, Durata, Grifols; Genentech; MedImmune, Merck, Medicines Co; Pfizer, Novartis, Novadigm, Theravance; xBiotech,
Speaker's Bureau	None
Employment	Duke University
Honoraria	Theravance; Green Cross
Membership on advisory committees or review panels, board membership,	Chair- Merck V710 Advisory Board Committee
Ownership Interest (e.g., stocks, stock options or other interests	NONE
Other relevant financial interests	Patent pending in sepsis diagnostic

Vaccine 30 (2012) 2921–2927

Contents lists available at SciVerse ScienceDirect

Vaccine

frontiers in IMMUNOLOGY

REVIEW ARTICLE
published: 24 March 2014
doi: 10.3389/fimmu.2014.00109

Covering all the bases: preclinical development of an effective *Staphylococcus aureus* vaccine

Ingrid L. Scully, Paul A. Liberator, Kathrin U. Jansen and Annaliesa S. Anderson*

Pfizer Vaccine Research and Development Unit, Pearl River, NY, USA

Review

Vaccine review: "*Staphyloccocus aureus* vaccines: Problems and prospects"

Kathrin U. Jansen*, Douglas Q. Girgenti, Ingrid L. Scully, Annaliesa S. Anderson

Departments of Medical Microbiology/Immunology and Medicine, University of Wisconsin School of Medicine and Public Health School, Madison

REVIEW

10.1111/1469-0691.12570

Where does a *Staphylococcus aureus* vaccine stand?

V. G. Fowler Jr[1] and R. A. Proctor[2]

1) Division of Infectious Diseases, Duke University Medical Center, Durham, NC, and 2) Department of Medical Microbiology/Immunology and Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Department of Pediatrics, Section of Infectious Diseases, The University of Chicago Medical Center, and Department of Medicine, Division of General Internal Medicine, Los Angeles Biomedical Research Institute at Harbor–University of California Los Angeles Medical Center

S. aureus Vaccines: State of the Art

- Many candidates have been developed
- All have failed
- We do not know why

Vaccine Target Antigens for Staphylococci

Staphvax, Altastaph (Nabi)
Pfizer, GSK (Belgium)

Arsanis, MedImmune

Secreted proteins

Cytoplasmic membrane

PIA
(differentially expressed)

V710 (Merck)
MntC (Pfizer)
Aurexis, Veronate (Inhibitex)

Cell surface protein
(tethered to cytoplasmic membrane)

Cell Surface protein
(Hydrophobically bound)

LPXTG Proteins

Transmembrane proteins
(eg porins and ABC transporters)

Lipoprotein
(tethered to cytoplasmic membrane)

Teichoic acids

Pagimaximab (Biosynexus)
Genentech

Types of *S. aureus* Immunotherapeutics

- Passive Immunization- Antibodies Given

  Treatment — *Treat existing infection*

  Prevention — *Prevent future infection*

- Active Immunization- Antibodies Produced

Compound	Product	Phase	Study design	Results
Passive immunization				
Treatment				
Aurexis Tefibazumab [87]	Humanized monoclonal anti-clumping factor A antibodies	II	Randomized, double-blind, placebo-controlled trial of standard treatment plus either Aurexis or placebo ($n = 63$)	No differences in adverse events or rate of death, relapse, or complications
Altastaph [88]	Pooled human anti-capsular polysaccharide (CP) types 5 and 8 antibodies	II	Randomized, double-blind, placebo-controlled trial of patients standard treatment plus Altastaph or placebo for *S. aureus* bacteraemia in adults ($n = 40$)	No significant mortality difference; shorter length of stay in Altastaph versus placebo (9 days versus 14 days; p 0.03)
Aurograb (not published in peer-reviewed journal)	Single-chain antibody variable fragment against ABC transporter component GrfA	II	Unpublished by sponsor	Addition of Aurograb to standard therapy for life-threatening staphylococcal infections failed to show efficacy
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Veronate [90]	Pooled human IgG to ClfA (*S. aureus*) and SdrG (*S. epidermidis*)	III	Double-blind, placebo-controlled trial of INH-21 versus placebo for prevention of staphylococcal late-onset sepsis in infants with birthweights 500–1250 g ($n = 1983$)	No difference in staphylococcal late-onset sepsis (5% INH-21 versus 6% placebo; p 0.34)
Pagimaximab [91]	Humanized mouse chimeric monoclonal antibody against lipoteichoic acid	II	Randomized, double-blind, placebo-controlled dose-ranging study for prevention of staphylococcal infection in patients with birthweight between 700 and 1300 g ($n = 88$)	Definite staphylococcal sepsis occurred in 0% (90 mg/kg), 20% (60 mg/kg), and 13% (placebo) (p 0.11). Findings not confirmed in Phase III trial
Active immunization				
StaphVax [58]	Bivalent vaccine of CP 5 and 8 conjugated individually to recombinant exoprotein A	III	Randomized, double-blind, placebo-controlled trial of StaphVax in prevention of *S. aureus* bacteraemia in haemodialysis dependent adults ($n = 1804$)	Efficacy in reduction of *S. aureus* bacteraemia at 54 weeks non-significant (p 0.23); post hoc efficacy estimate at 40 weeks: 57% (p 0.02)
V710 [2]	IsdB	III	Randomized, double-blind, placebo-controlled, event trial of efficacy of V710 to prevent major *S. aureus* infection in adults undergoing median sternotomy ($n = 8031$)	Study stopped prematurely by data monitoring committee. No significant efficacy. Vaccine recipients who developed *S. aureus* infection were five times more likely to die than control recipients who developed *S. aureus* infection (23.0 versus 4.2 per 100 person-years

Fowler & Proctor *ClinVaccine Immunol* 2014

Passive

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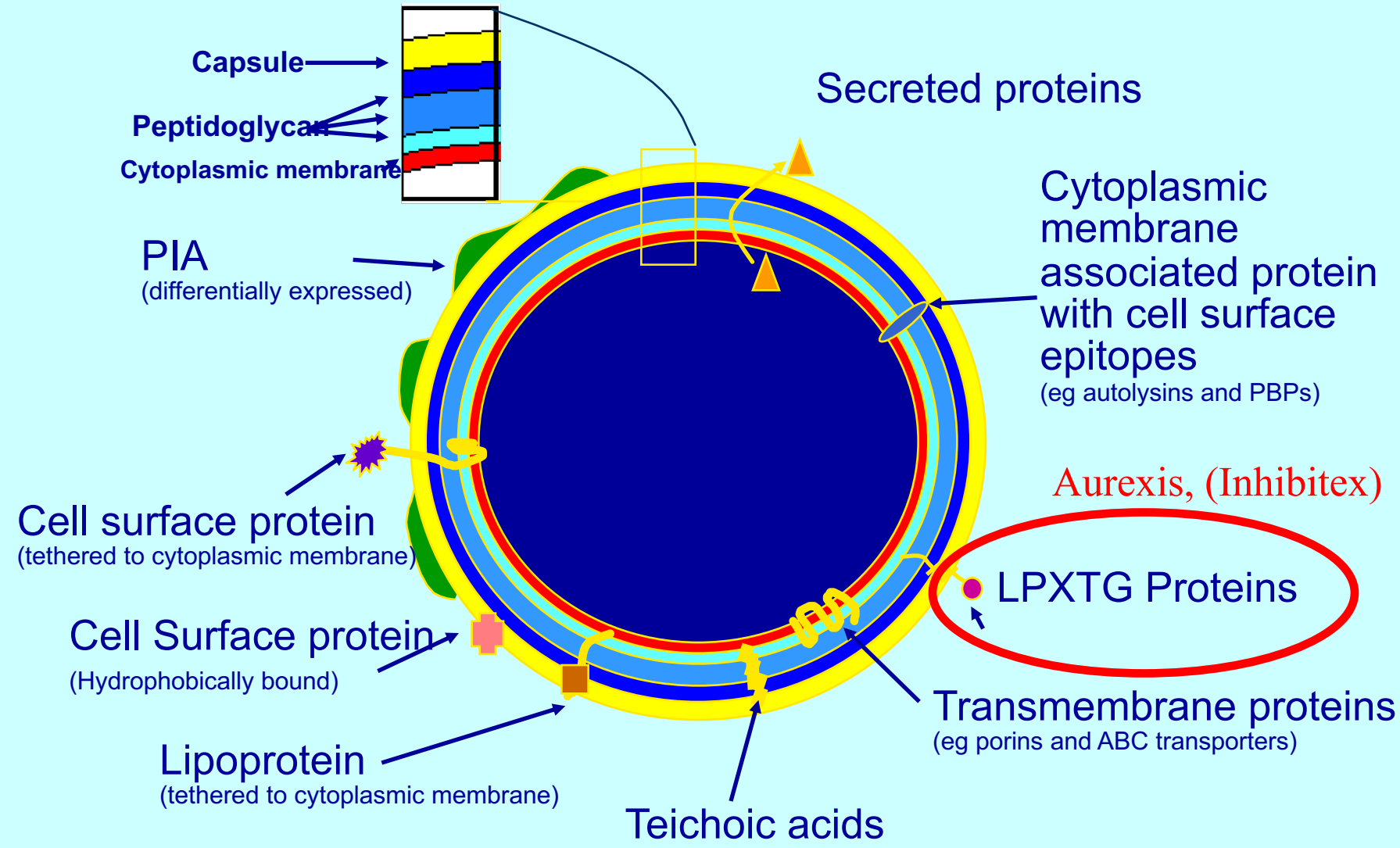
Fowler & Proctor *ClinVaccine Immunol* 2014

Aurexis

Vaccine Target Antigens for Staphylococci



Phase II, Randomized, Double-Blind, Multicenter Study Comparing the Safety and Pharmacokinetics of Tefibazumab to Placebo for Treatment of *Staphylococcus aureus* Bacteremia

J. John Weems, Jr.,[1] James P. Steinberg,[2]† Scott Filler,[3] John W. Baddley,[4] G. Ralph Corey,[5] Priya Sampathkumar,[6] Lisa Winston,[7] Joseph F. John,[8] Christine J. Kubin,[9] Rohit Talwani,[10] Thomas Moore,[11]‡ Joseph M. Patti,[12] Seth Hetherington,[12]* Michele Texter,[12] Eric Wenzel,[12] Violet A. Kelley,[12] and Vance G. Fowler, Jr.[5]

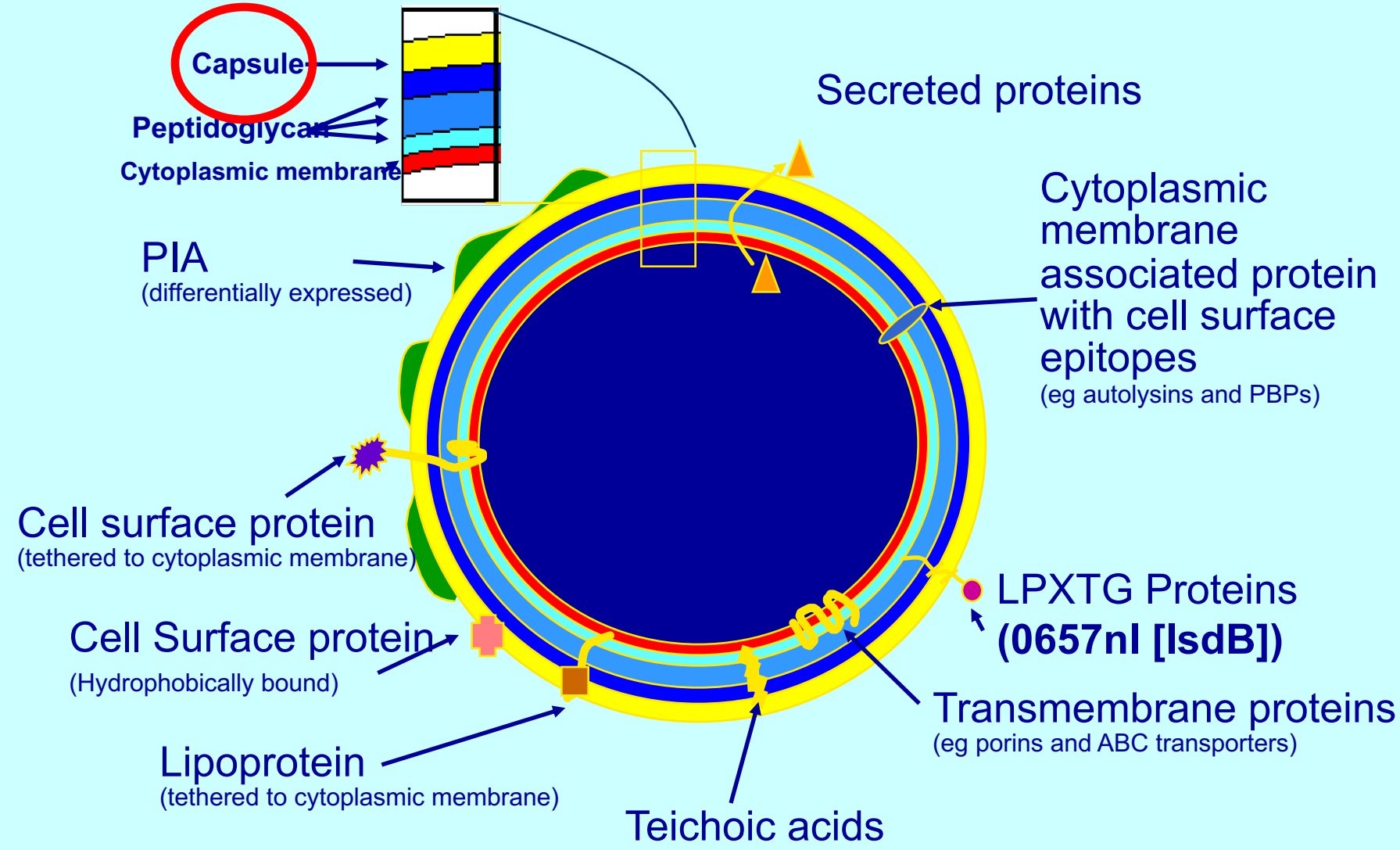
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2006, p. 2751–2755

- Aurexis (Tefibazumab) Humanized monoclonal antibodies against Clumping Factor A
- Prevents Binding of *S. aureus* to Fibrinogen, no Killing Activity
- Randomized, double-blinded, placebo-controlled trial of 60 patients with *S. aureus* bacteremia
- Standard therapy + Aurexis v. Standard therapy + Placebo
- Efficacy: No significant difference in Composite endpoint or Severity Progression
- SAEs: 2 Possible, one definite (Hypersensitivity)

Altastaph

Vaccine Target Antigens for Staphylococci

Staphvax, (Altastaph)



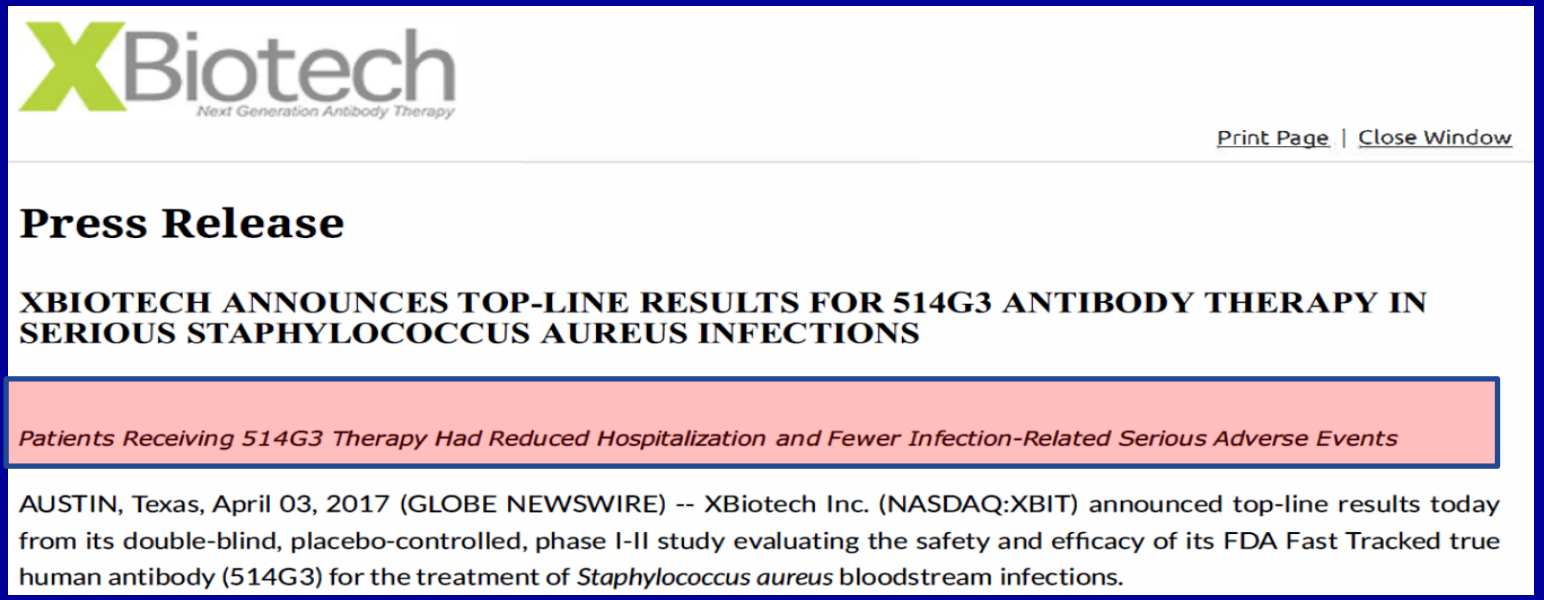
Phase II, Randomized, Multicenter, Double-Blind, Placebo-Controlled Trial of a Polyclonal Anti-*Staphylococcus aureus* Capsular Polysaccharide Immune Globulin in Treatment of *Staphylococcus aureus* Bacteremia▽

Mark E. Rupp,[1]* H. Preston Holley, Jr.,[2] Jon Lutz,[3] Peter V. Dicpinigaitis,[4] Christopher W. Woods,[5,7] Donald P. Levine,[6] Naomi Veney,[2] and Vance G. Fowler, Jr.[7]

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2007, p. 4249–4254

- Pooled human antibodies against *S. aureus* capsule 5 and 8
- Randomized, double-blinded, placebo-controlled trial of 40 patients with *S. aureus* bacteremia
- Standard therapy + Altastaph v. Standard therapy + Placebo
- Efficacy: Mortality higher in Altastaph (23% v. 11%; p=0.42)
  Shorter time to afebrile (2 v. 7d; p=0.09)
  Shorter hospitalization (9 v. 14d; p=0.03)
- SAEs: 95% of Drug-related Events were in Altastaph

Xbiotech 514G3



XBiotech
Next Generation Antibody Therapy

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Press Release

XBIOTECH ANNOUNCES TOP-LINE RESULTS FOR 514G3 ANTIBODY THERAPY IN SERIOUS STAPHYLOCOCCUS AUREUS INFECTIONS

Patients Receiving 514G3 Therapy Had Reduced Hospitalization and Fewer Infection-Related Serious Adverse Events

AUSTIN, Texas, April 03, 2017 (GLOBE NEWSWIRE) -- XBiotech Inc. (NASDAQ:XBIT) announced top-line results today from its double-blind, placebo-controlled, phase I-II study evaluating the safety and efficacy of its FDA Fast Tracked true human antibody (514G3) for the treatment of *Staphylococcus aureus* bloodstream infections.

- Epitope: *"… a key virulence determinant of S. aureus"*
- Design: *Phase I/II Dose Finding, Double-blind RCT*
- Sample Size: *n=36 study vs n= 16 Placebo*
- Results:
  - ↓ *Hospitalization (8.6d vs 12.7d; p=0.092)*
  - ↓ *S. aureus-related SAEs (11% vs 25%; p=0.23)*
  - ↑ **Mortality (11% vs 0%; p=0.30)**

Passive

Prevention

Compound	Product	Phase	Study design	Results
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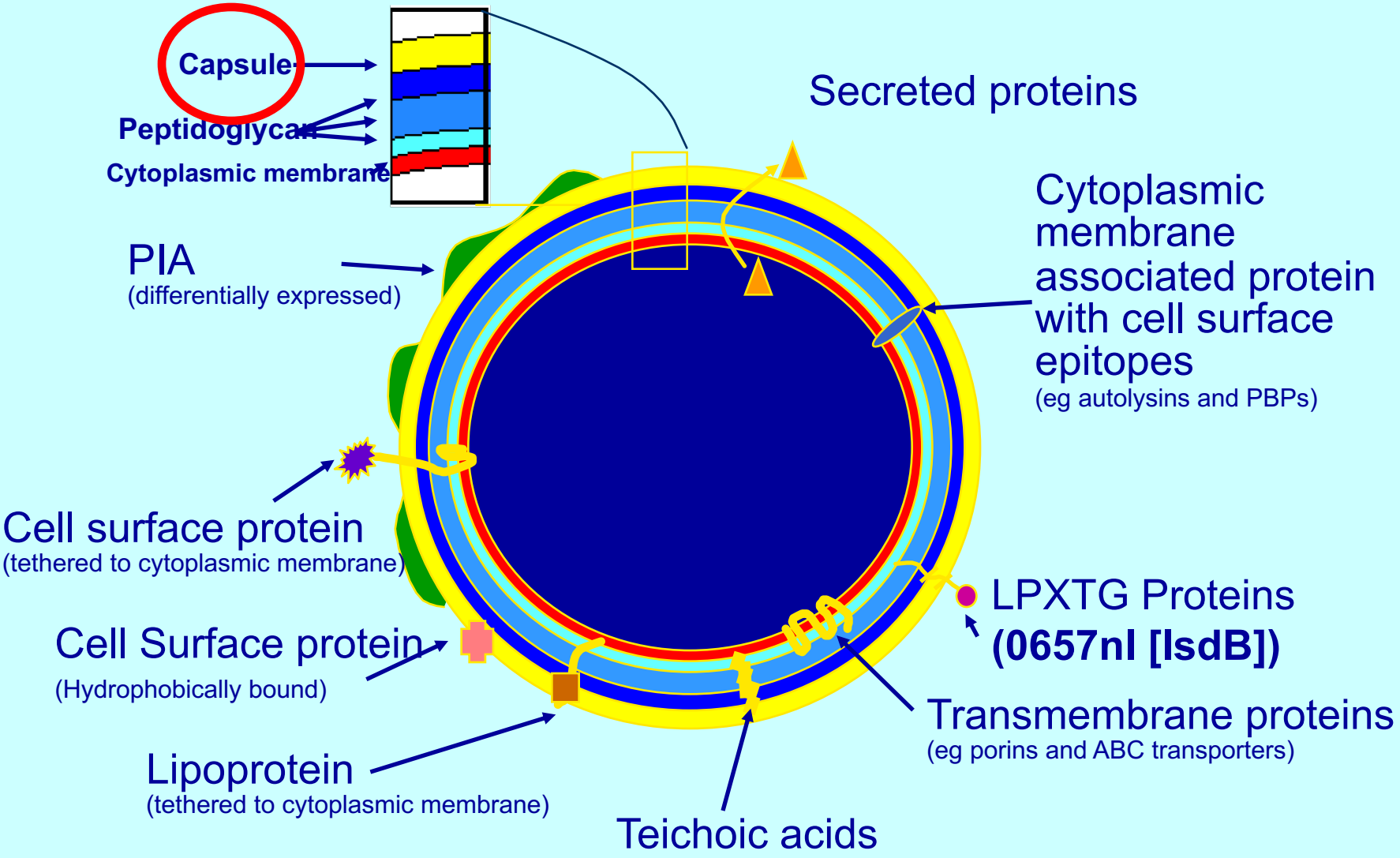
Fowler & Proctor *ClinVaccine Immunol* 2014

Altastaph

Vaccine Target Antigens for Staphylococci

Altastaph (Nabi)



A blinded, randomized, multicenter study of an intravenous *Staphylococcus aureus* immune globulin

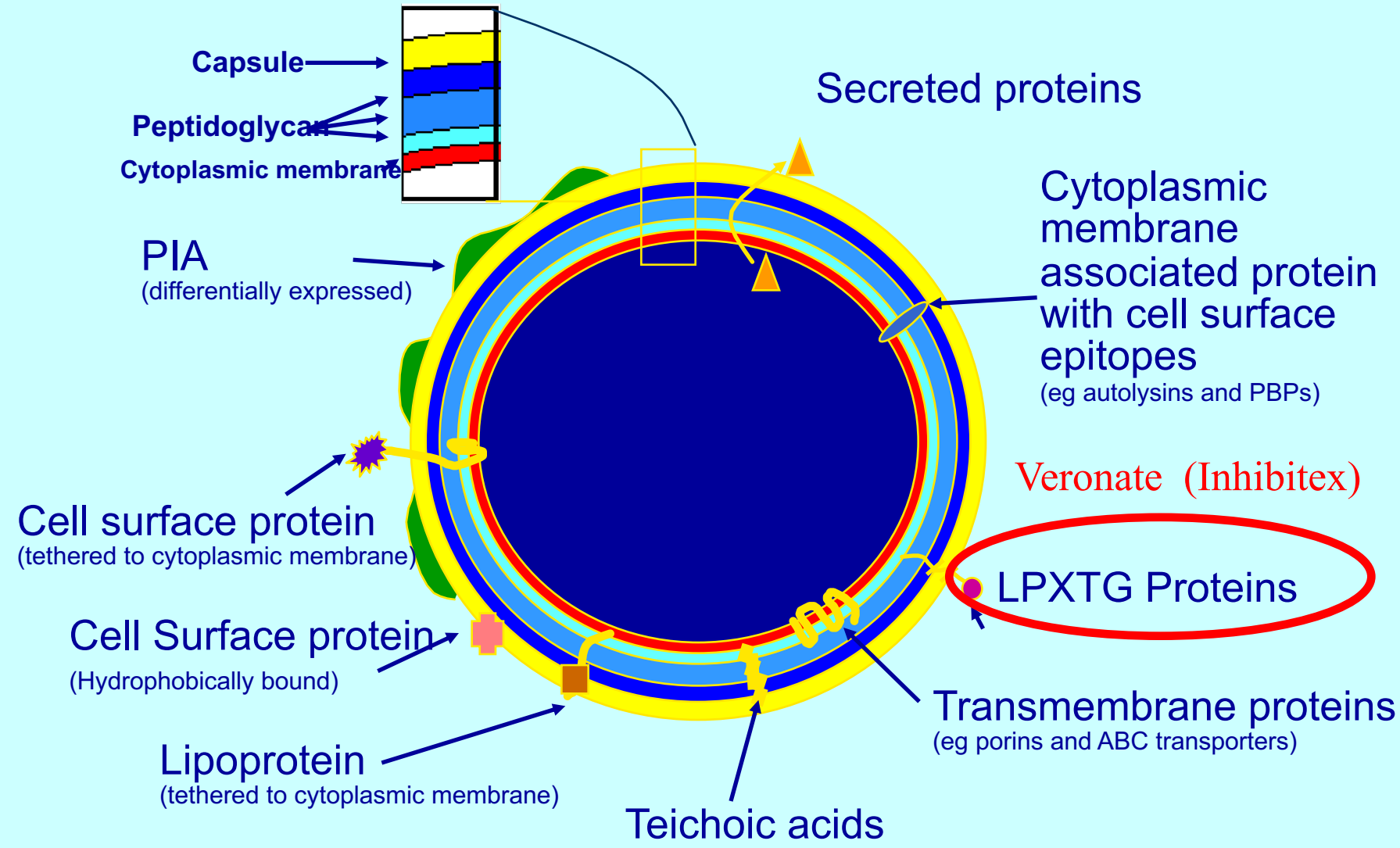
DK Benjamin Jr[1,12], R Schelonka[2], R White[3], HP Holley Jr[4], E Bifano[5], J Cummings[6], K Adcock[7], D Kaufman[8], B Puppala[9], P Riedel[10], B Hall[11], J White[12] and CM Cotten[1] on behalf of the *S. aureus* prevention investigators[13]

Journal of Perinatology (2006) 26, 290–295

- Pooled human antibodies against *S. aureus* capsule 5 and 8
- Phase II Randomized, double-blinded, placebo-controlled trial of 206 Very Low Birth Weight Infants
- Infusion resulted in hight levels of specific S. aureus type 5 & 8 capsular polysaccharide IgG
- No difference in episodes of SAB among the two groups
- Adverse events similar in both arms

Veronate

Vaccine Target Antigens for Staphylococci



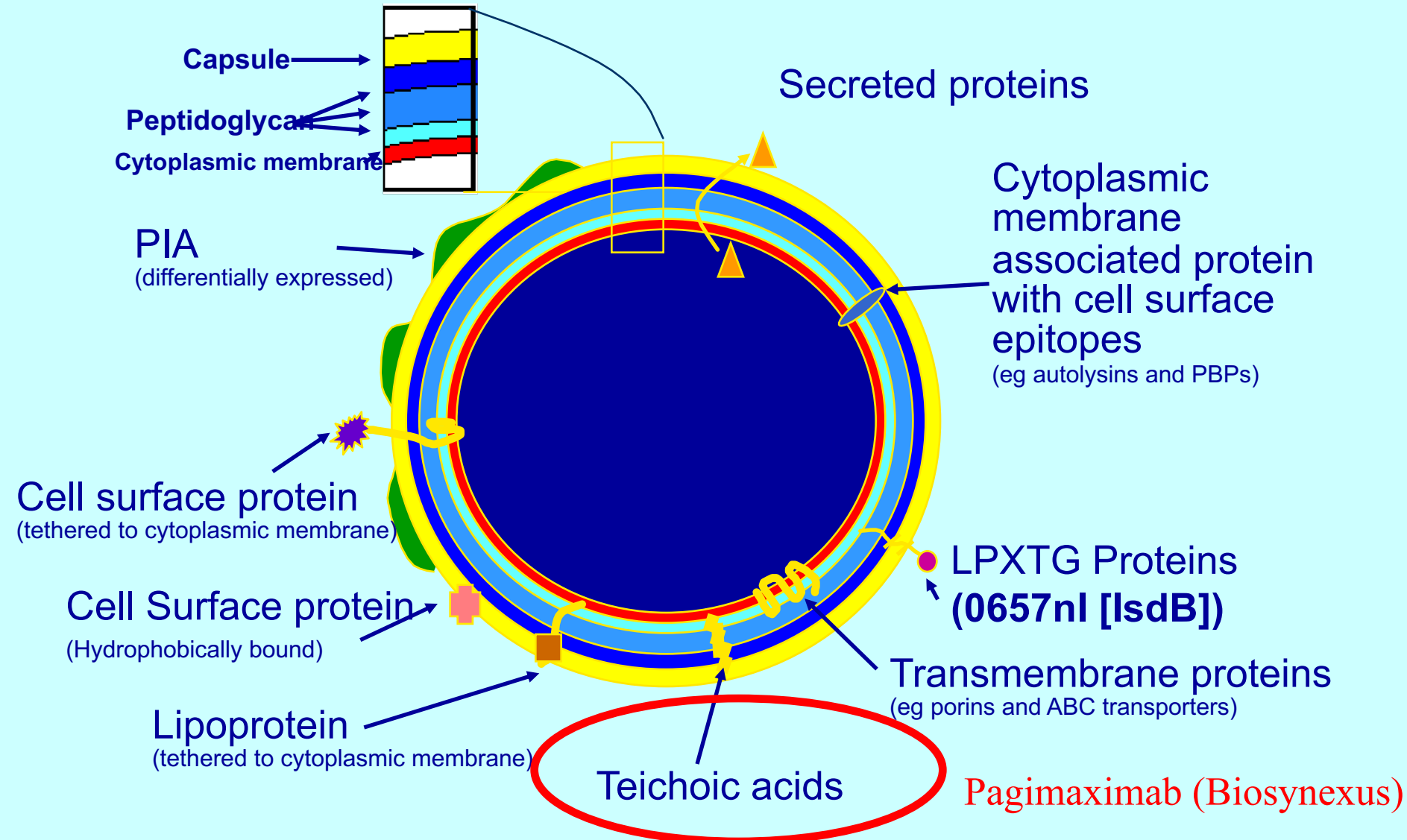
Clinical Trial of Safety and Efficacy of IHN-A21 for the Prevention of Nosocomial Staphylococcal Bloodstream Infection in Premature Infants

***The Journal of Pediatrics* 2007; 151:260-265**

- Pooled human IgG to ClfA (*S. aureus*) & SdrG (*S. epidermidis*)
- Double-blind, placebo-controlled trial of INH-21 v. placebo for prevention of staphylococcal late onset sepsis in 1983 infants with birth weight 500g-1250g
- No difference in episodes of late-onset staphylococcal sepsis

Pagibaximab

Vaccine Target Antigens for Staphylococci



A Randomized Study of a Monoclonal Antibody (Pagibaximab) to Prevent Staphylococcal Sepsis

Leonard E. Weisman, Helen M. Thackray, Robin H. Steinhorn, William F. Walsh, Herbert A. Lassiter, Ramasubbareddy Dhanireddy, Beverly S. Brozanski, Kristine G. H. Palmer, Michael S. Trautman, Marilyn Escobedo, H. Cody Meissner, Pontthenkandath Sasidharan, Jennifer Fretz, John F. Kokai-Kun, William G. Kramer, Gerald W. Fischer and James J. Mond

Pediatrics 2011;128:271–279

- Human chimeric monoclonal antibody against *S. aureus* lipoteichoic acid
- Phase II dose-ranging randomized, double blind placebo controlled trial of 88 patients with birth weight 700-1300g and age 2-5 days
- Non-significant difference in rates of staphylococcal sepsis
  0% (90mg/kg), 20% (60mg/kg),13% (placebo) (p=0.11)
- Results not confirmed in Phase III (unpublished)

Active

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Fowler & Proctor *ClinVaccine Immunol* 2014

Staphvax

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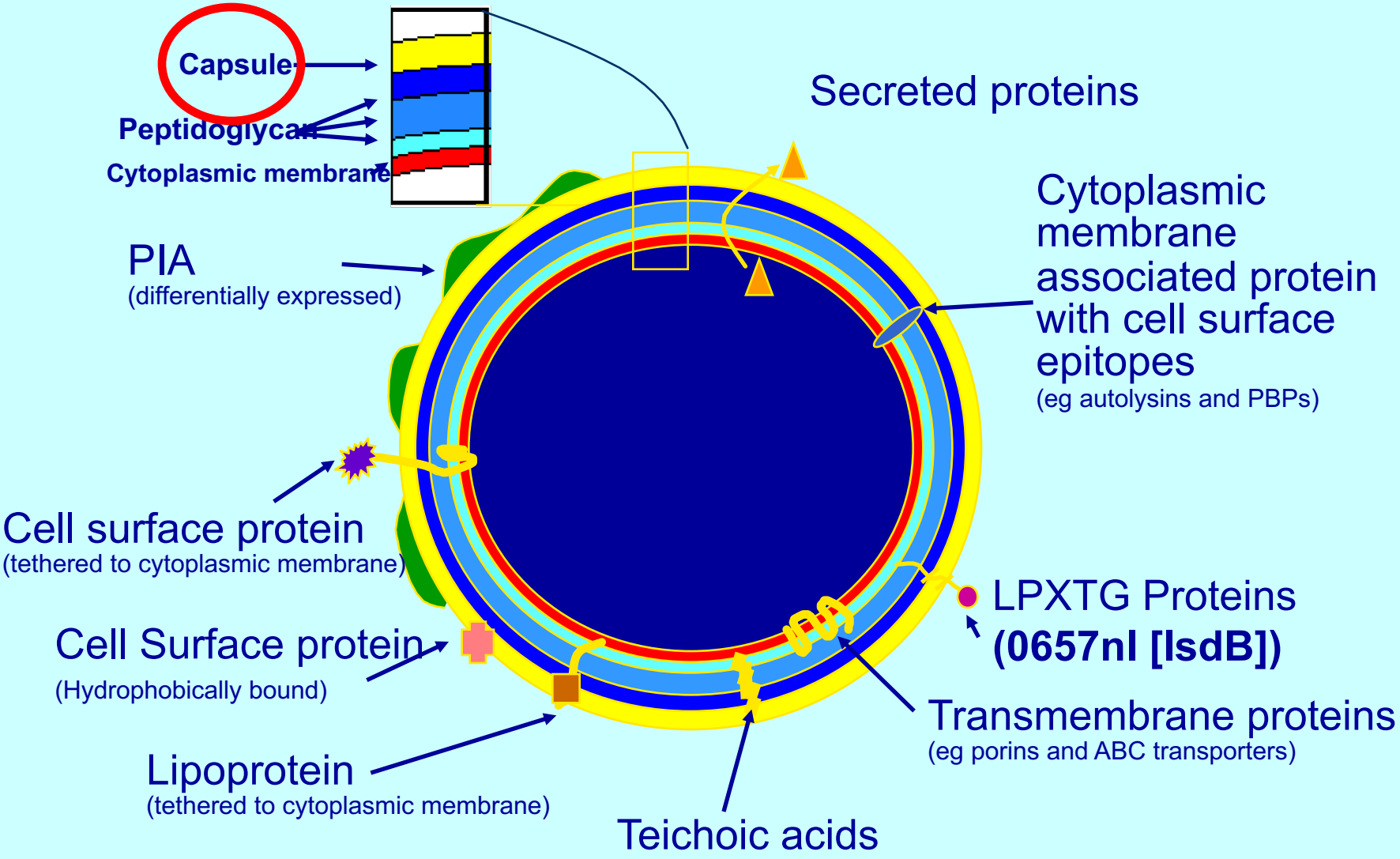


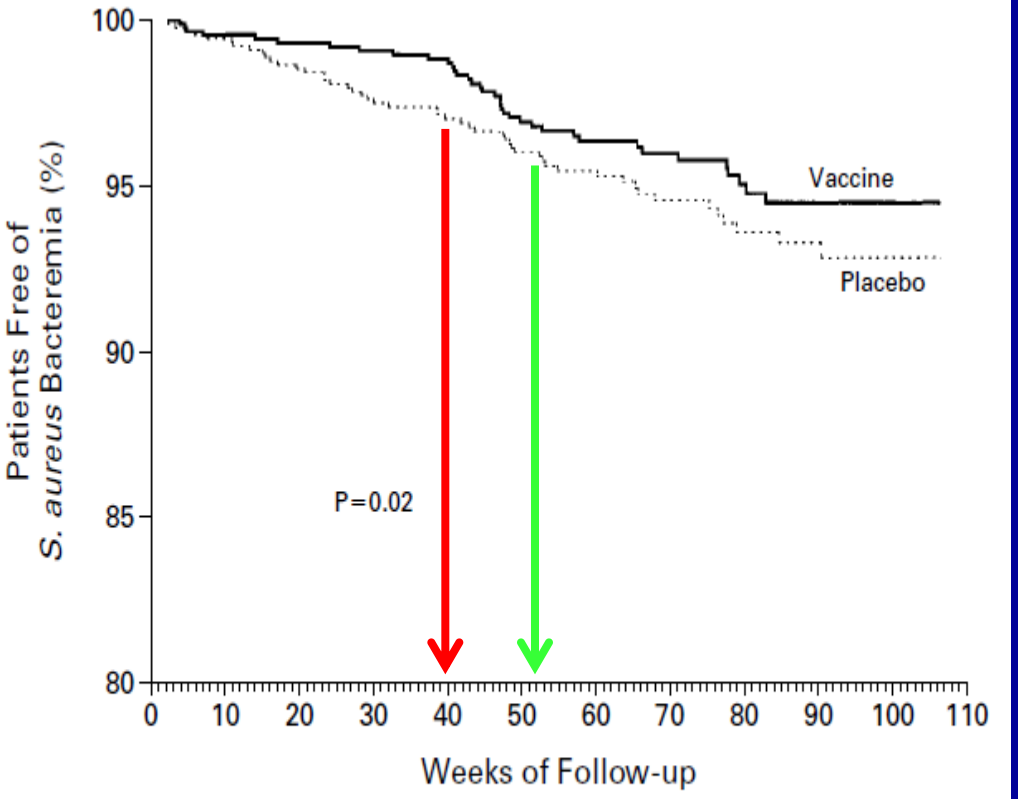
USE OF A *STAPHYLOCOCCUS AUREUS* CONJUGATE VACCINE IN PATIENTS RECEIVING HEMODIALYSIS

HENRY SHINEFIELD, M.D., STEVEN BLACK, M.D., ALI FATTOM, PH.D., GARY HORWITH, M.D., SCOTT RASGON, M.D., JUAN ORDONEZ, M.D., HOCK YEOH, M.D., DAVID LAW, M.D., JOHN B. ROBBINS, M.D., RACHEL SCHNEERSON, M.D., LARRY MUENZ, PH.D., AND ROBERT NASO, PH.D.

N Engl J Med 2002;346:491-6

- Capsule types 5 & 8 (~80-85% of clinical isolates)
- Double-blinded, placebo-controlled, randomized trial in 1,804 hemodialysis patients
- Gortex graft or Primary Fistula (Cuffed tunneled catheter dialysis recipients excluded)
- *a priori* endpoint : reduction in events of *S. aureus* bacteremia set at 54 weeks

Efficacy of StaphVax – A Question of Timing?



No. at Risk	Week						
	0	13	26	52	54	78	104
Vaccine	892	870	843	705	667	380	15
Placebo	906	889	850	710	661	369	10

Weeks after Injection	Vaccine Group		Placebo Group		Efficacy (95% CI)	P Value
	No. Infected	Person-Years	No. Infected	Person-Years		
					%	
10	4	135.2	5	138.0	18 (−28 to 84)	1.0
20	6	300.6	13	306.6	53 (−33 to 85)	0.17
30	8	461.9	22	469.7	63 (14 to 86)	0.02
40	11	618.9	26	627.0	57 (10 to 81)	0.02
50	25	766.5	34	775.3	26 (−28 to 58)	0.30
54	27	818.4	37	827.4	26 (−24 to 57)	0.23
91	37	1165.0	49	1161.6	25 (−18 to 52)	0.24

N Engl J Med 2002;346:491-6.

Repeat Phase III Trial - Failure

Randomized, double-blinded, placebo-controlled trial of 3,600 patients on hemodialysis

- Endpoint set at 6 months
- Results: No reduction in *S. aureus* types 5 and 8 infections in the StaphVAX group
- Withdrew Marketing Authorization Application (MAA) to market StaphVAX in the European Union

PIPELINE

Pipeline Overview

Transplant

Transplant Overview

Nabi-HB® Intravenous & HEBIG™

Civacir®

ATG-Fresenius S

Nicotine Addiction

NicVAX®

Gram-Positive Programs

Gram-positive Overview

StaphVAX®-Pentavalent

Altastaph®

EnteroVAX™

S. epidermidis (PS-1 and GP-1)

Hematology And Oncology

Nabi® Anti-D

Anti-viral

RENS

StaphVAX®-Pentavalent (Staphylococcal Polysaccharide Conjugate and Toxoid Vaccine)

We have placed this program on hold for further clinical development pending partnership or external funding of the program.

Vaccines and antibody therapies represent a new and innovative approach in broadening the available clinical tools against the global health problem of healthcare-associated bacterial infections. This approach is focused on effective prevention whenever possible and using a combination approach of antibiotics with antibodies to treat serious infection.

We have advanced the development of StaphVAX® (*Staphylococcus aureus* Polysaccharide Conjugate Vaccine) for use in patients who are at high risk of *S. aureus* infection and who are able to respond to a vaccine by producing their own antibodies. StaphVAX is an investigational polysaccharide conjugate vaccine based on patented technology that we have licensed from the Public Health Service/National Institute of Health (NIH). In its initial formulation, it contained surface polysaccharides found in the outer coating of Types 5 and 8 *S. aureus* bacteria. To produce the vaccine, the polysaccharide molecules are linked, or conjugated, to a non-toxic, carrier protein derived from the bacteria *Pseudomonas aeruginosa* (Pseudomonas exoprotein A) that causes a strong response by the immune system to the conjugated complex. Once given the vaccine, the patient's immune system produces antibodies, to the polysaccharides, which should bind to *S. aureus* upon subsequent exposure to the bacteria. These antibodies help the immune system to eliminate the *S. aureus* bacteria before significant damage can be inflicted. Since these antibodies bind to several sites on the bacteria's surface polysaccharides, we believe that it will be much more difficult for the bacteria to develop resistance to the antibodies.

Our next-generation StaphVAX® (Staphylococcal Polysaccharide Conjugate and Toxoid Vaccine) vaccine and antibody products, will contain *S. aureus* Type 336 antigen combined with *S. aureus* Types 5 and 8 antigens, as well as two other

HOME SEARCH CONTACTS

MEDIA INVESTORS

DONORS

RESOURCES

Key Facts About *Staphylococcus aureus* Infections

Request Product/Medical Information

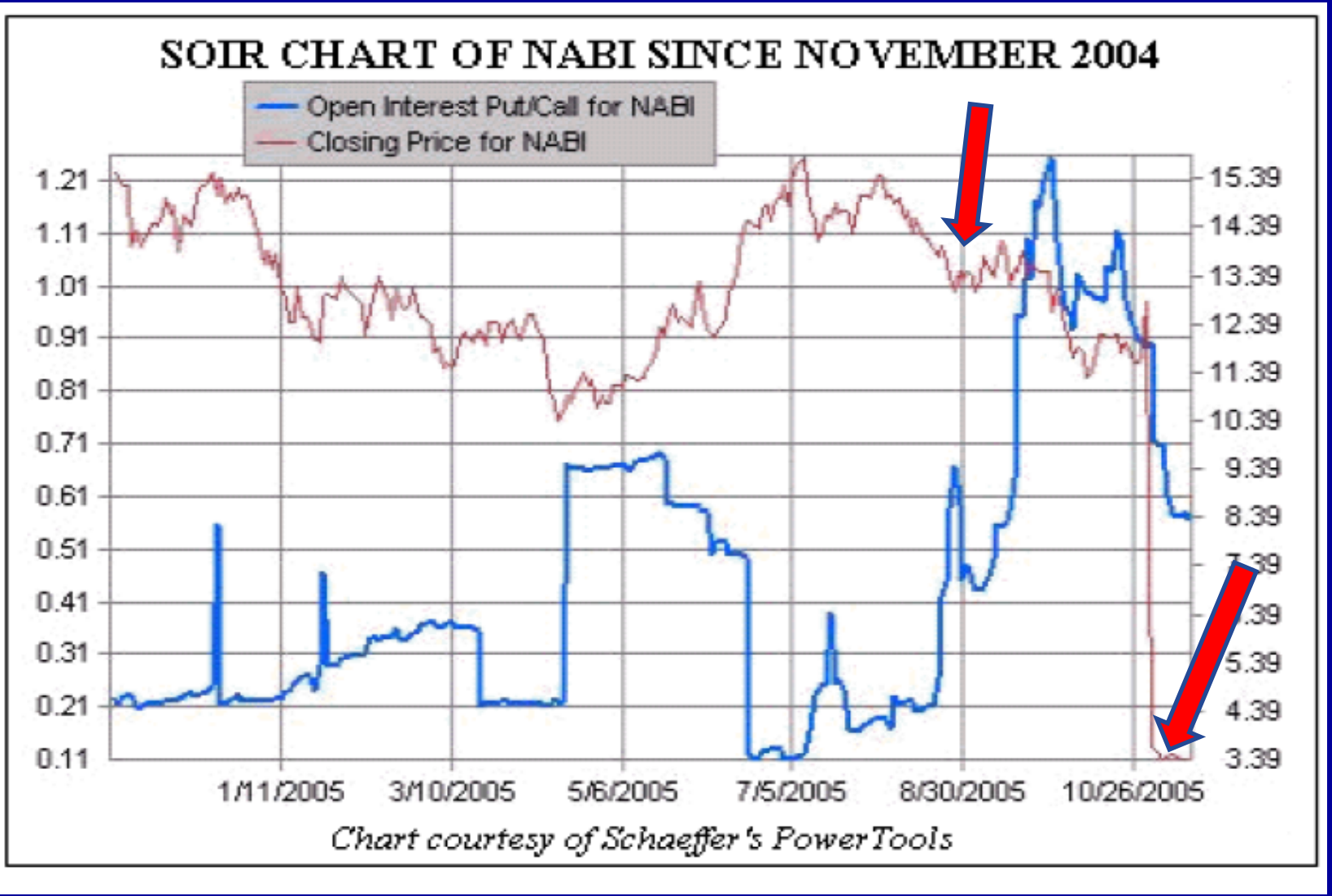
LATEST NEWS

February 7, 2007
Nabi Biopharmaceuticals Announces Positive Phase I Results from its *S. epidermidis* PS-1 and *S. aureus* Type 336 Vaccine Clinical Trials

March 21, 2006
Nabi Biopharmaceuticals Announces Completion of Outside Advisory Panel Assessment of Gram-Positive Program - Development of

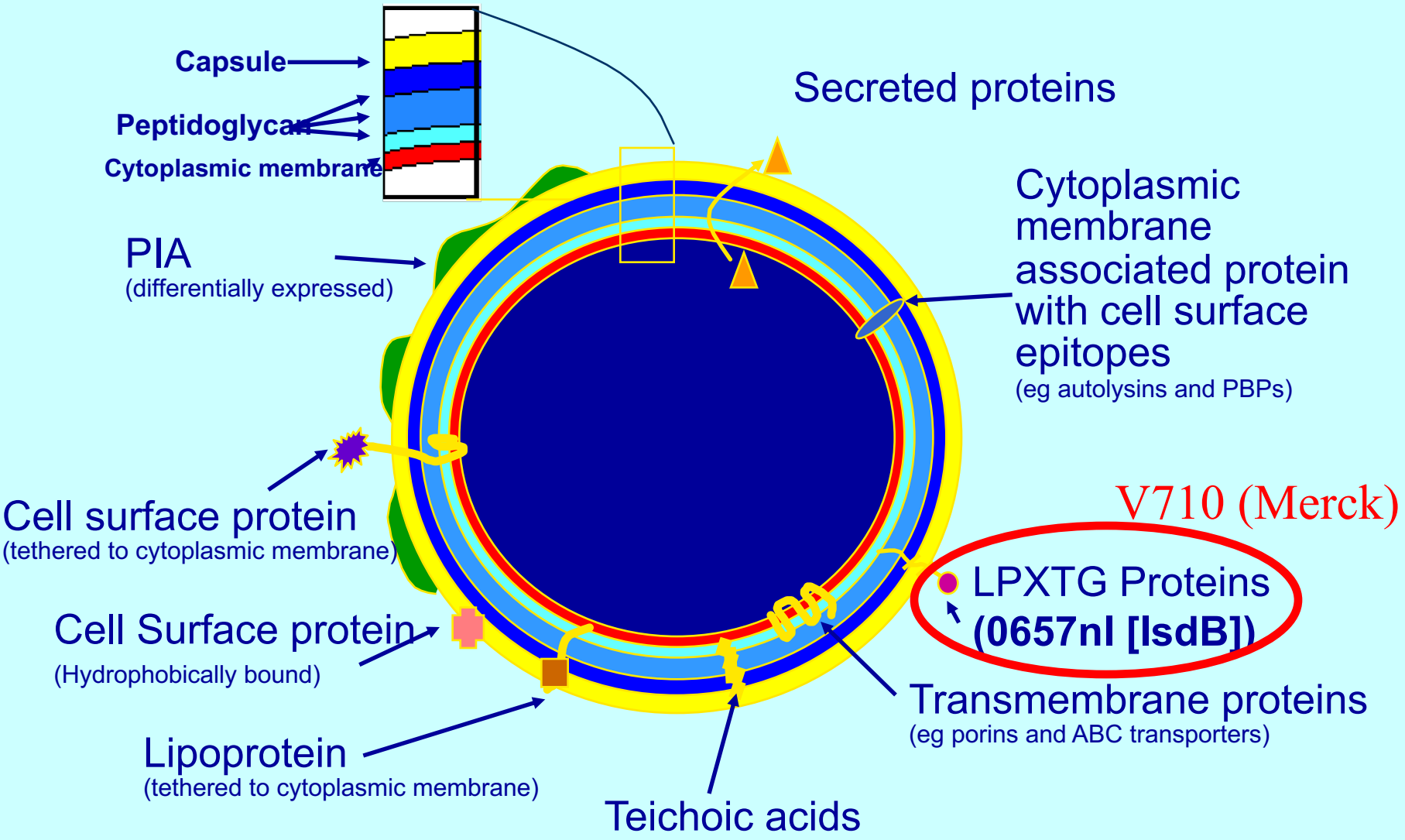
Source: http://www.nabi.com/pipeline/pipeline.php?id=1

Nabi Stock Price Before and After Staphvax Announcement



V710

Vaccine Target Antigens for Staphylococci



ORIGINAL CONTRIBUTION

Effect of an Investigational Vaccine for Preventing *Staphylococcus aureus* Infections After Cardiothoracic Surgery

A Randomized Trial

Vance G. Fowler Jr, MD, MHS
Keith B. Allen, MD
Edson D. Moreira Jr, MD, MPH, PhD
Moustafa Moustafa, MD
Frank Isgro, MD
Helen W. Boucher, MD
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Robert Betts, MD
Jonathan S. Hartzel, PhD
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Tessie B. McNeely, PhD
Nicholas A. Kartsonis, MD
Dalya Guris, MD
Matthew T. Onorato, BS
Steven S. Smugar, MD
Mark J. DiNubile, MD
Ajoke Sobanjo-ter Meulen, MD, MSc

Importance Infections due to *Staphylococcus aureus* are serious complications of cardiothoracic surgery. A novel vaccine candidate (V710) containing the highly conserved *S aureus* iron surface determinant B is immunogenic and generally well tolerated in volunteers.

Objective To evaluate the efficacy and safety of preoperative vaccination in preventing serious postoperative *S aureus* infection in patients undergoing cardiothoracic surgery.

Design, Setting, and Participants Double-blind, randomized, event-driven trial conducted between December 2007 and August 2011 among 8031 patients aged 18 years or older who were scheduled for full median sternotomy within 14 to 60 days of vaccination at 165 sites in 26 countries.

Intervention Participants were randomly assigned to receive a single 0.5-mL intramuscular injection of either V710 vaccine, 60 μg (n=4015), or placebo (n=4016).

Main Outcome Measures The primary efficacy end point was prevention of *S aureus* bacteremia and/or deep sternal wound infection (including mediastinitis) through postoperative day 90. Secondary end points included all *S aureus* surgical site and invasive infections through postoperative day 90. Three interim analyses with futility assessments were planned.

Results The independent data monitoring committee recommended termination of the study after the second interim analysis because of safety concerns and low efficacy. At the end of the study, the V710 vaccine was not significantly more efficacious than placebo in preventing either the primary end points (22/3528 V710 vaccine recipients [2.6 per 100 person-years] vs 27/3517 placebo recipients [3.2 per 100 person-years]; relative risk, 0.81; 95% CI, 0.44-1.48; *P*=.58) or secondary end points despite eliciting robust antibody responses. Compared with placebo, the V710 vaccine was associated with more adverse experiences during the first 14 days after vaccination (1219/3958 vaccine recipients [30.8%;

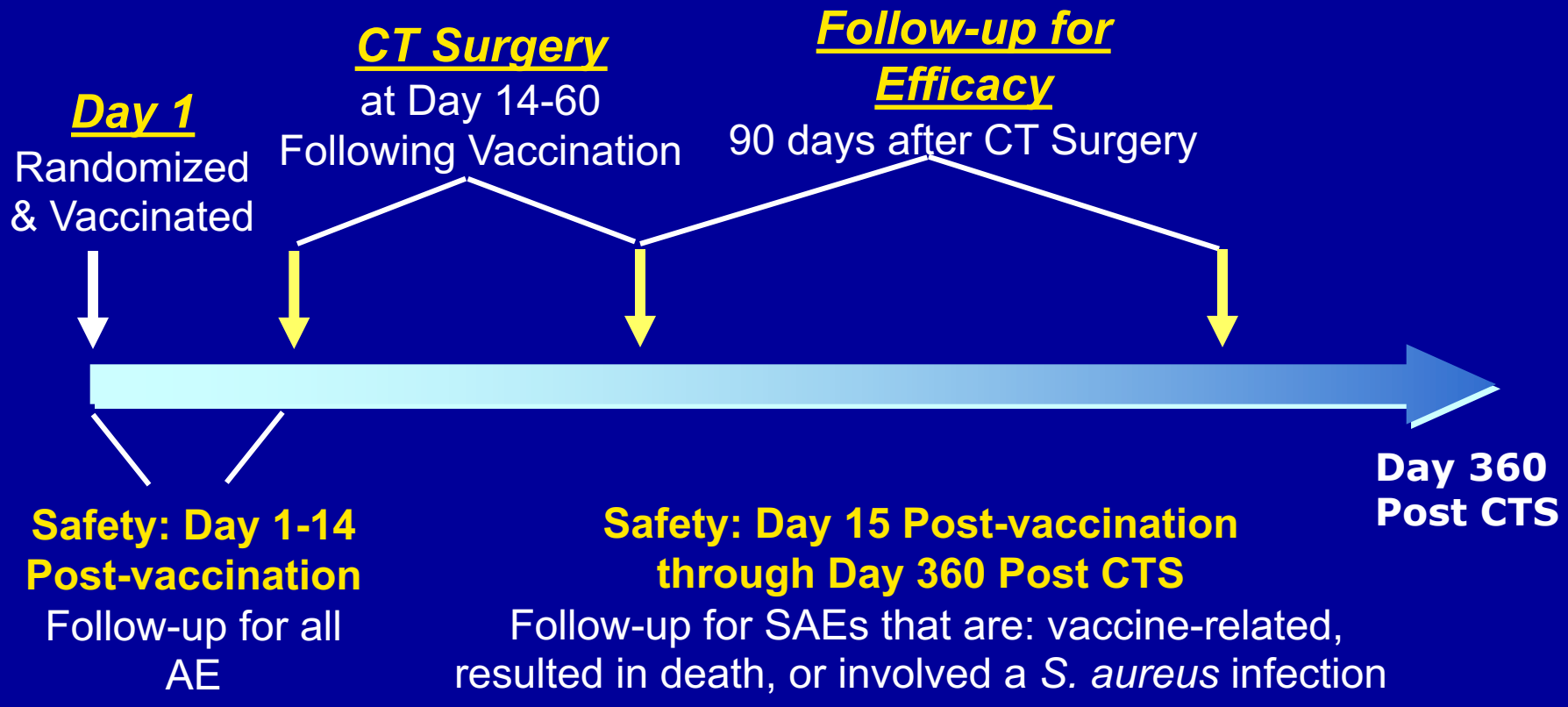
JAMA. 2013;309(13):1368-1378

Merck Candidate *S. aureus* Vaccine Antigen: Iron Surface Determinant B (IsdB)

- IsdB of *S. aureus*
  - expressed and highly conserved in all *S. aureus* strains tested
  - immunogenic during acute *S. aureus* infections
- V710 vaccine
  - protective in 3 different murine models
  - well tolerated and immunogenic in Phase I studies

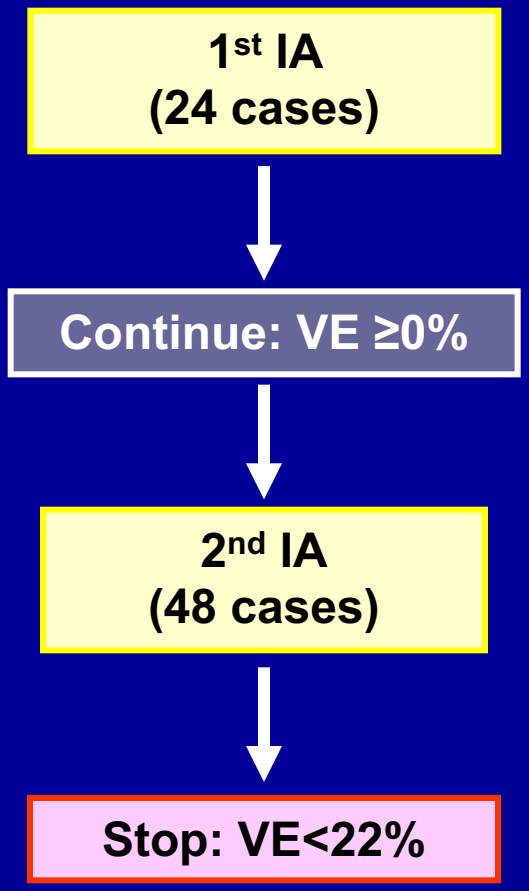
Palazzolo-Ballance, *J Immunol* 2008
Miajilovic, *Microbiology* 2010
Kuklin, *Infect & Immunity* 2006
Harro, *JID* 2010 and *Vaccine* 2012

V710-003 Study Design: Overview



V710-003 Interim Analyses (IA)

Event-driven study, with 3 planned IA to assess vaccine futility



1st IA [Jan 2010] to assess for futility →
Passed: Vaccine Efficacy (VE) = 59%

2nd IA [Apr 2011]

Study discontinued due to concerns about safety and low efficacy

Baseline Characteristics: Demographics

Randomized	V710 Group N = 4005	Placebo Group N = 4005
Male	2676 (67)	2,670 (67)
White	3088 (77)	3063 (76)
Age, median (range), years	65 (18-91)	66 (19-93)
STS Score, median (range)	6 (0-29)	6 (0-26)
BMI >30 kg/M^2	1108 (28)	1027 (26)
Diabetes Mellitus	963 (24)	961 (24)
Nasal Colonization with *S. aureus*	738 (18)	714 (18)
Positive for MRSA	72 (2)	65 (2)
Cardiothoracic surgery	3822 (96)	3840 (96)
CABG only	1198 (31)	1247 (32)
Valve replacement/repair (w/ or w/o CABG)	1927 (50)	1909 (50)
Other	697 (18)	684 (18)
Time of Surgery, median (IQR) days post-vaccine	24 (18-37)	24 (18-36)

Analysis of *S. aureus* Infections

	V710 60mcg	Placebo	Vaccine Efficacy (%) (95% CI)	p-Value (one-sided)
Number of Subjects Randomized	4005	4005		
Number of Subjects Randomized and Vaccinated	3981	3982		
Number of Subjects included in the Primary Efficacy Population	3528	3517		
Primary Hypothesis				
Number of *S. aureus* Bacteremia and/or DSWI infections	22 (0.6)	27 (0.8)	18.5 (-48.6, 55.8)	0.584
✓ *Bacteremia*	15 (0.4)	21 (0.6)	28.6	------
✓ *DSWI - Mediastinitis*	9 (0.3)	9 (0.3)	0.0	------
✓ *DSWI - Deep Incisional SSI Involving the Sternal Wound*	7 (0.2)	9 (0.3)	22.2	------
MSSA	11 (0.3)	19 (0.5)	42.1	------
MRSA	11 (0.3)	8 (0.2)	-37.5	------

Safety Analysis: Duration of Study

	V710 60mcg N=3,958			Placebo N=3,967			V710 60mcg - Placebo	
	n	Total Follow-Up Time (Person-Yrs)	Estimated Rate (per 100-Person-Yrs)	n	Total Follow-Up Time (Person-Yrs)	Estimated Rate (per 100-Person-Yrs)	Estimated Rate Difference (95% CI)	p-value
With serious AEs	291	3468.9	8.4	274	3493.4	7.8	0.5 (-0.8, 1.9)	0.424
With serious AEs involving the diagnosis of *S. aureus*	49	3523.0	1.4	57	3535.2	1.6	-0.2 (-0.8, 0.4)	0.448
Who died	201	3550.3	5.7	177	3567.9	5.0	0.7 (-0.4, 1.8)	0.200
With MOF	31	3553.1	0.9	17	3571.4	0.5	0.4 (0.0, 0.8)	0.042

Analysis of Mortality and Multi-Organ Failure (MOF) in Subjects with *S. aureus* Infections

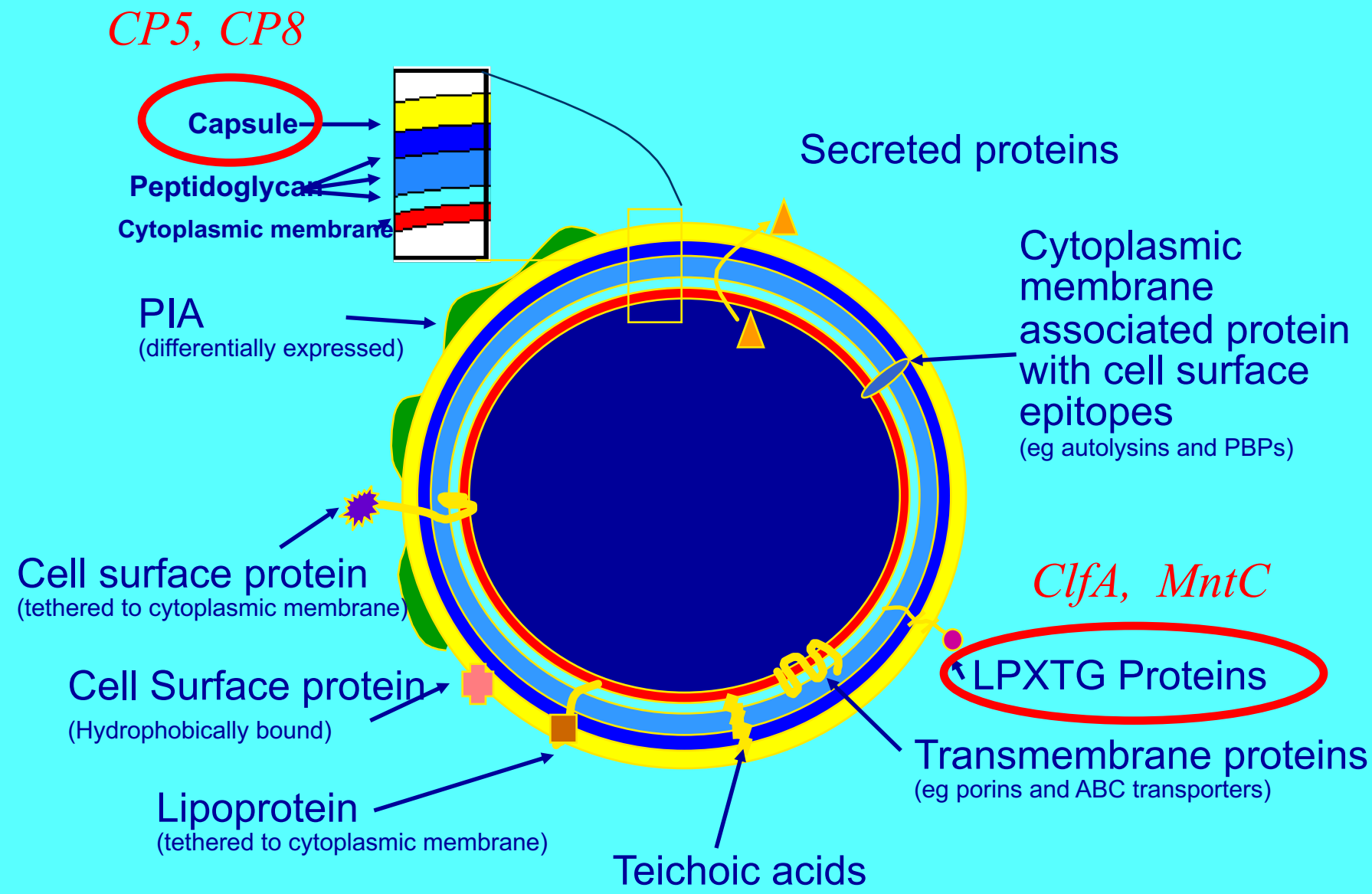
Primary Endpoints	V710 60mcg			Placebo			V710 60mcg - Placebo
	n	Total Follow-Up Time (Person-Yrs)	Estimated Rate (per 100-Person-Yrs)	n	Total Follow-Up Time (Person-Yrs)	Estimated Rate (per 100-Person-Yrs)	Estimated Rate Difference (95% CI)
Subjects with *S. aureus* bacteremia and/or DSWI	**23**			**28**			
Who died	7	19.6	35.7	2	25.7	7.8	28.0 (2.0, 66.7)
Who died due to MOF	3	20.2	14.9	0	25.9	0.0	14.9 (0.0, 43.7)
Subjects with any *S. aureus* infections	**73**			**96**			
Who died	15	65.2	23.0	4	94.4	4.2	18.8 (8.0, 34.1)
Who died with MOF	5	65.9	7.6	0	94.5	0.0	7.6 (3.2, 17.8)

Conclusions

- V710 was not efficacious in preventing *S. aureus* bacteremia and/or deep sternal wound infection
  - Despite eliciting a robust antibody response
- Similar overall vaccine & placebo mortality
- V710 was associated with multi-organ failure
- V710 recipients who developed *S. aureus* infection were ~ 5 times more likely to die than placebo recipients who developed *S. aureus* infection
- Causality not established

Pfizer

Vaccine Target Antigens for Staphylococci



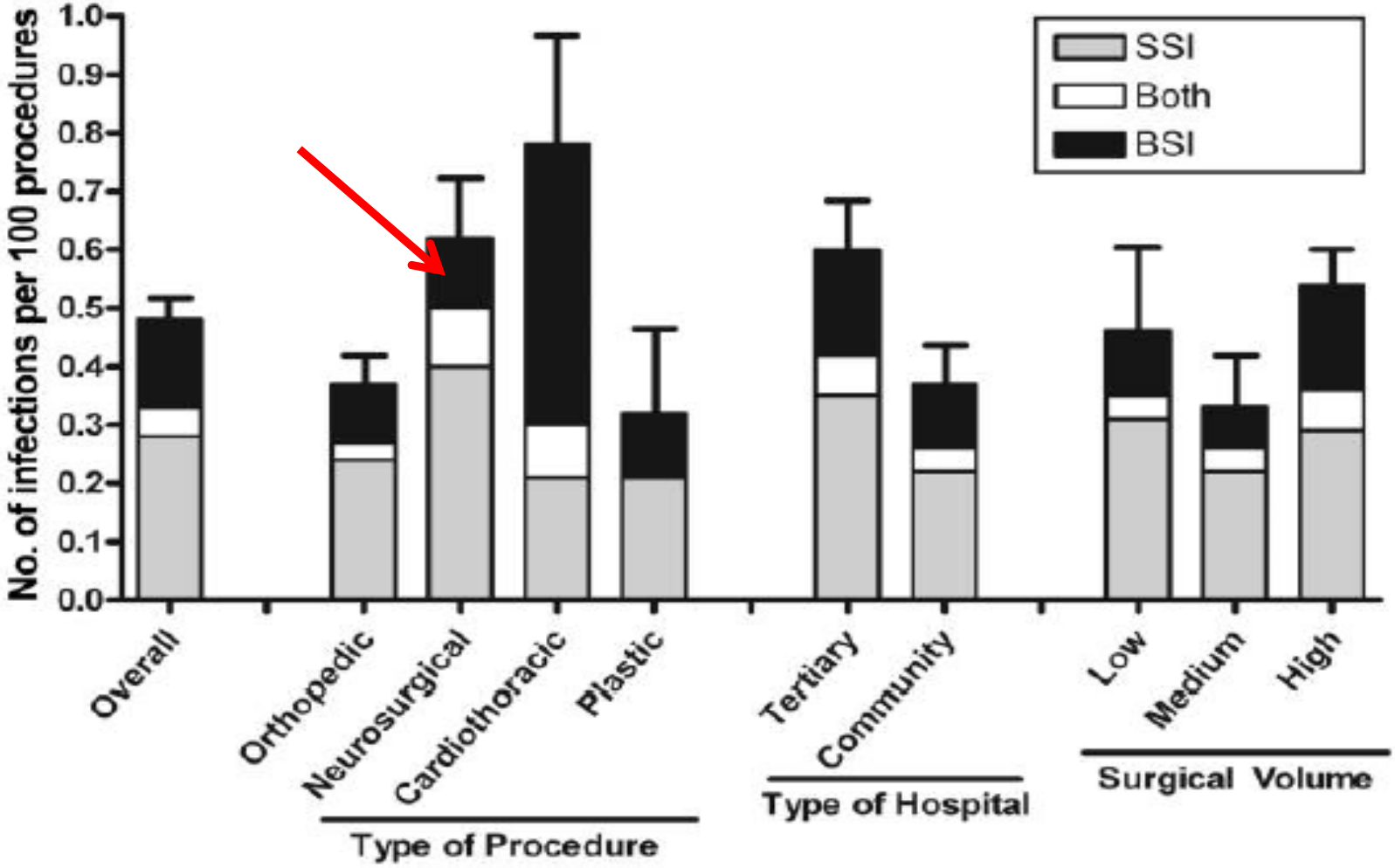
Published on *Pfizer Pharmaceutical News and Media | Pfizer: the world's largest research-based pharmaceutical company* (http://press.pfizer.com) on 7/7/15 8:00 am EDT

Pfizer Begins Phase 2b Study Of Its Investigational Multi-antigen Staphylococcus aureus Vaccine In Adults Undergoing Elective Spinal Fusion Surgery

Release Date:
Tuesday, July 7, 2015 8:00 am EDT

- 4 Antigens:
  - *CP5 & CP8 Conjugated to Carrier CRM197*
  - *ClfA (Recombinant)*
  - *MntC*
- 2600 patients
- 1° Endpoint: Postop *S. aureus* Bloodstream infection and/or deep incisional or organ/space surgical site infections within 90d

Why Spinal Surgery?



Infect Control Hosp Epidemiol 2010; 31(7):701-709


Three Strikes, YOU'RE OUT!

Why do the Trials Fail?
Three Possibilities

1) Good Vaccine, Bad Trial

2) Good Vaccine, Bad Assumption

3) No Good Vaccine for *S. aureus*

Why do the Trials Fail?

Three Possibilities

1) Good Vaccine, Bad Trial

2) Good Vaccine, Bad Assumption

3) No Good Vaccine for *S. aureus*

1. Good Vaccine, Bad Trial

Phase II, Randomized, Double-Blind, Multicenter Study Comparing the Safety and Pharmacokinetics of Tefibazumab to Placebo for Treatment of *Staphylococcus aureus* Bacteremia

J. John Weems, Jr.,[1] James P. Steinberg,[2]† Scott Filler,[3] John W. Baddley,[4] G. Ralph Corey,[5] Priya Sampathkumar,[6] Lisa Winston,[7] Joseph F. John,[8] Christine J. Kubin,[9] Rohit Talwani,[10] Thomas Moore,[11]‡ Joseph M. Patti,[12] Seth Hetherington,[12]* Michele Texter,[12] Eric Wenzel,[12] Violet A. Kelley,[12] and Vance G. Fowler, Jr.[5]

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2006, p. 2751–2755

Phase II, Randomized, Multicenter, Double-Blind, Placebo-Controlled Trial of a Polyclonal Anti-*Staphylococcus aureus* Capsular Polysaccharide Immune Globulin in Treatment of *Staphylococcus aureus* Bacteremia▽

Mark E. Rupp,[1]* H. Preston Holley, Jr.,[2] Jon Lutz,[3] Peter V. Dicpinigaitis,[4] Christopher W. Woods,[5,7] Donald P. Levine,[6] Naomi Veney,[2] and Vance G. Fowler, Jr.[7]

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2007, p. 4249–4254

Novartis Stops Development of Aurograb
Drug Discovery & Development - September 02, 2008

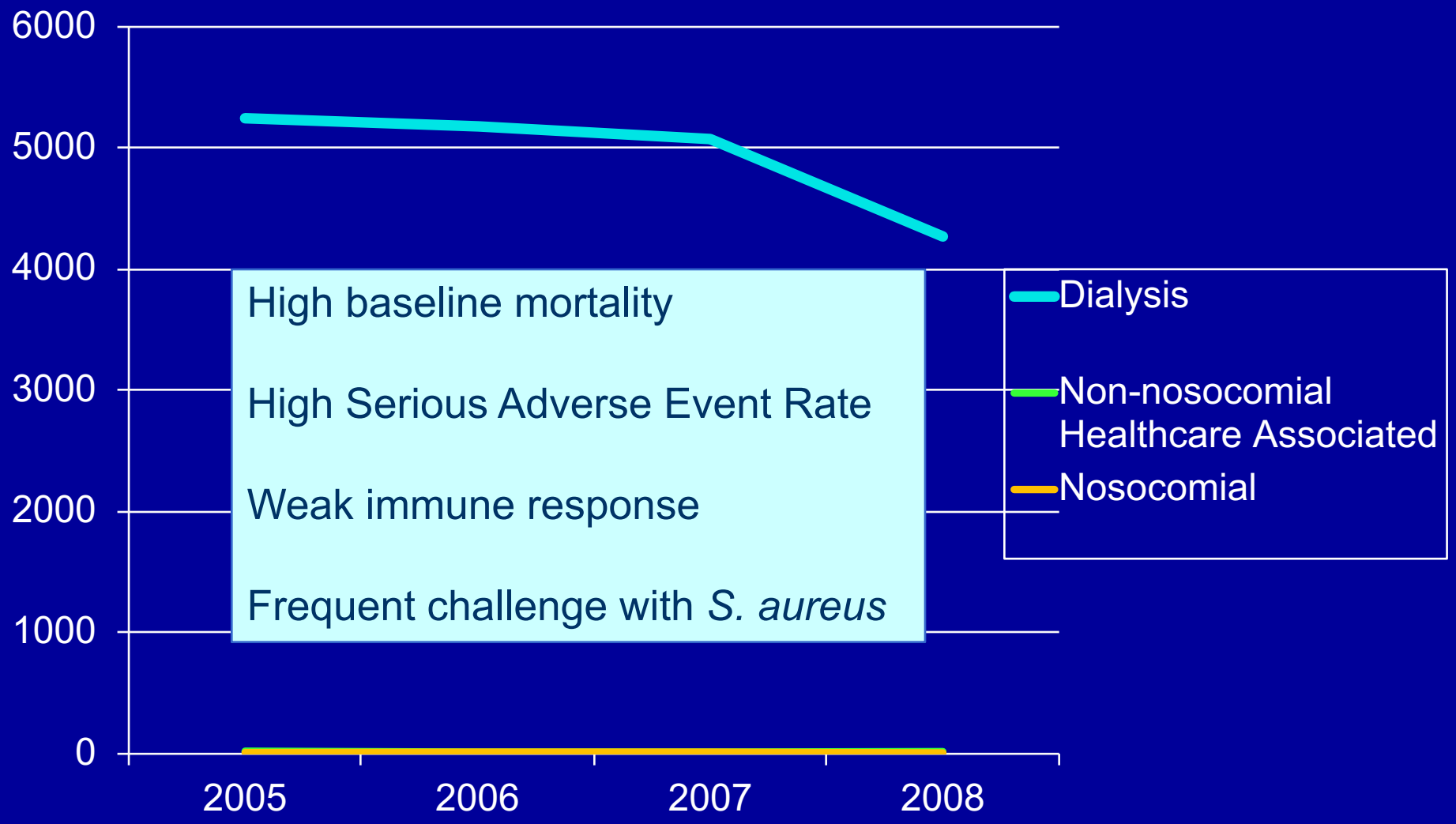
Novartis has decided not to pursue further development of the pharmaceuticals pipeline project Aurograb, an add-on therapy to antibiotics that was being assessed for use in treating deep-seated staphylococcal infections, following a review of recent Phase II clinical data showing a lack of efficacy.

Why Would Smart Companies Put a Good Vaccine in the Wrong Clinical Trial?

	Prevention Trial	Treatment Trial
Sample Size	2000-8000+	~ 300
Complexity	Multinational, Hundreds of sites	All US ≤ 30 sites
Timing	3-5y	1-2y

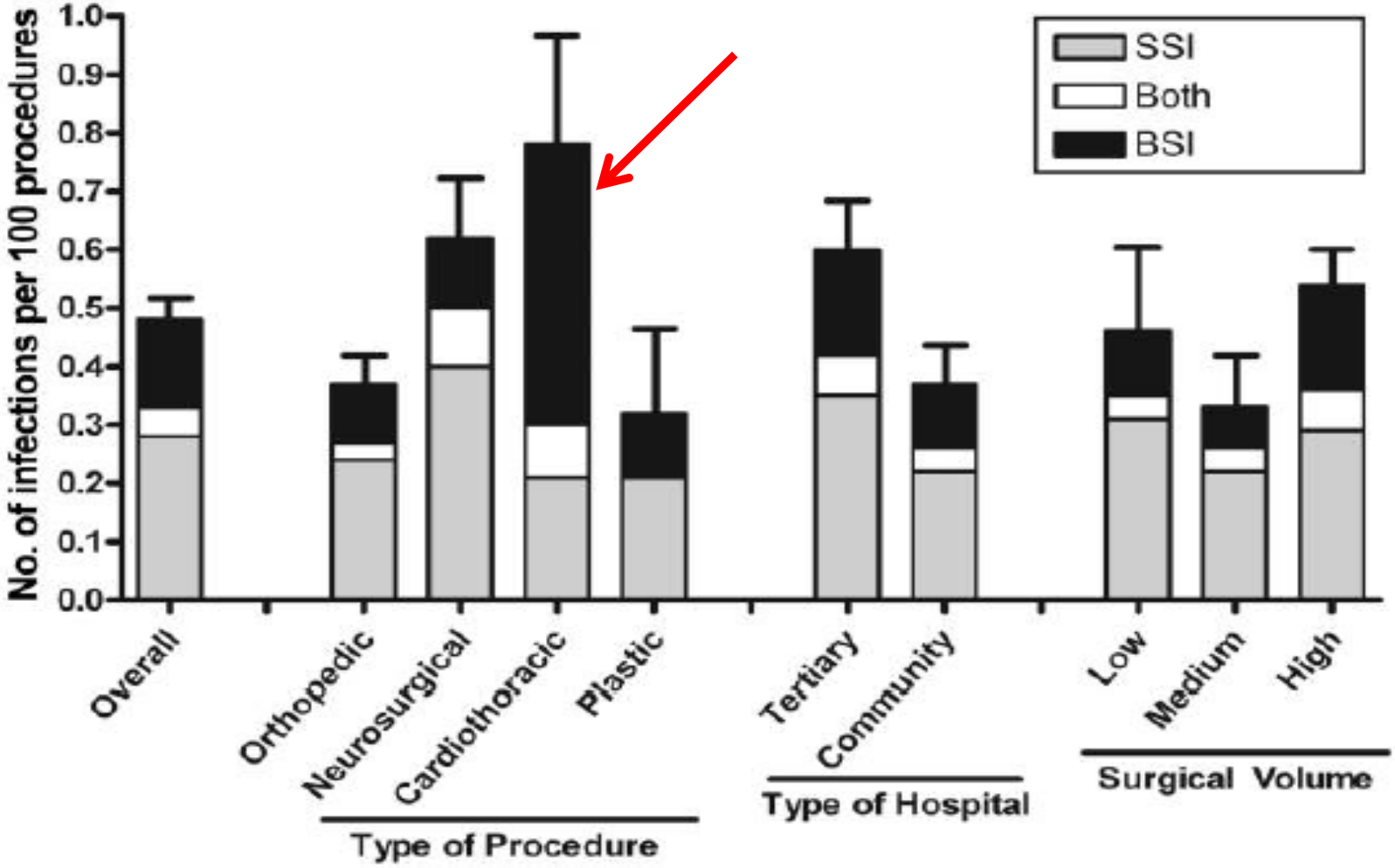
Why Hemodialysis?

Incidence of Invasive MRSA per 100,000 Person-Years



JAMA. 2010;304(6):641-648

Why Cardiac Surgery?



Infect Control Hosp Epidemiol 2010; 31(7):701-709

Problem with Cardiac Surgery: ↑ Risk ≈ ↓ Sample Size

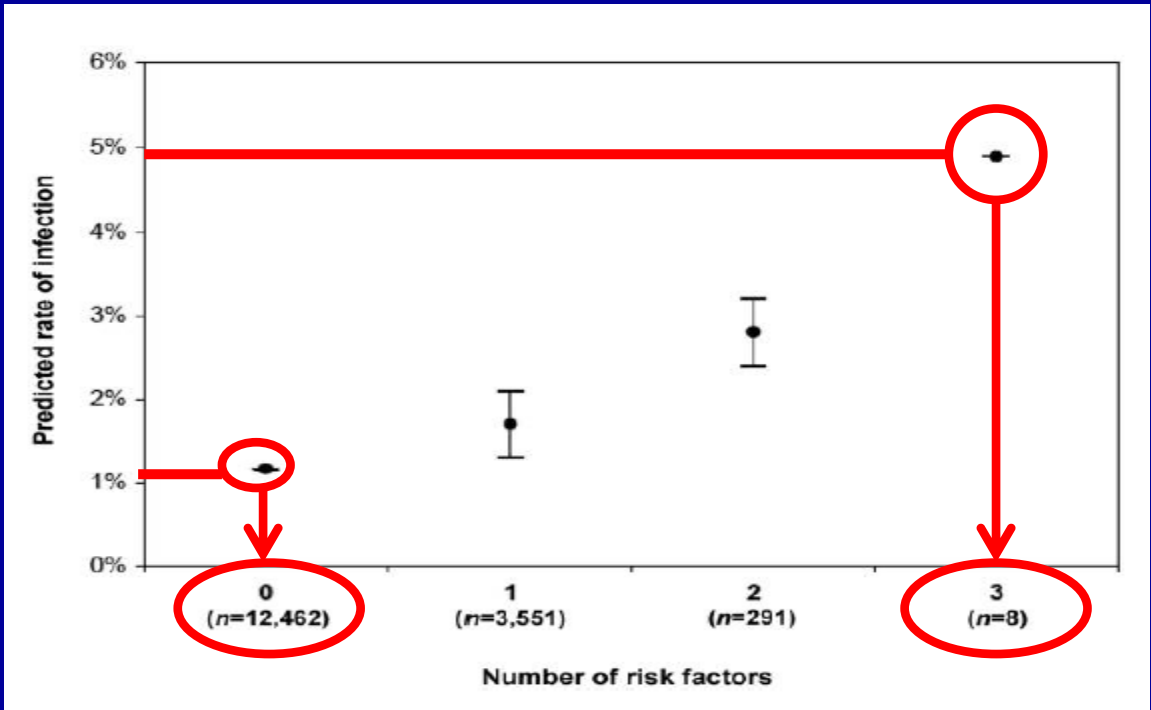


TABLE 3. Multivariable Models of Preoperative Risk Factors for Major Types of *Staphylococcus aureus* Infection at 90 Days After Surgery, for Patients at 8 Medical Centers, 2000–2004

Patient, variable	*S. aureus* bacteremia aOR (95% CI)	*S. aureus* bacteremia or chest wound infection aOR (95% CI)
Patients specifically coded for median sternotomy or imputed[a]		
BMI >40	2.24 (1.16–4.33)	1.87 (1.10–3.19)
Chronic renal failure	2.13 (1.19–3.80)	1.76 (1.06–2.90)
Chronic lung disease	2.01 (1.36–2.95)	1.42 (1.02–1.98)
Valve repair or replacement	1.44 (1.01–2.04)	…
Old age	1.02 (1.01–1.04)	…
Patients specifically coded for median sternotomy[b]		
Chronic lung disease	2.04 (1.26–3.30)	…
Valve repair or replacement	1.80 (1.16–2.81)	…
BMI >40	…	2.27 (1.16–4.46)
BMI 30–40	…	1.60 (1.11–2.32)

Infect Control Hosp Epidemiol 2009; 30:242-248

Why do the Trials Fail?
Three Possibilities

1) Good Vaccine, Bad Trial

2) Good Vaccine, Bad Assumption

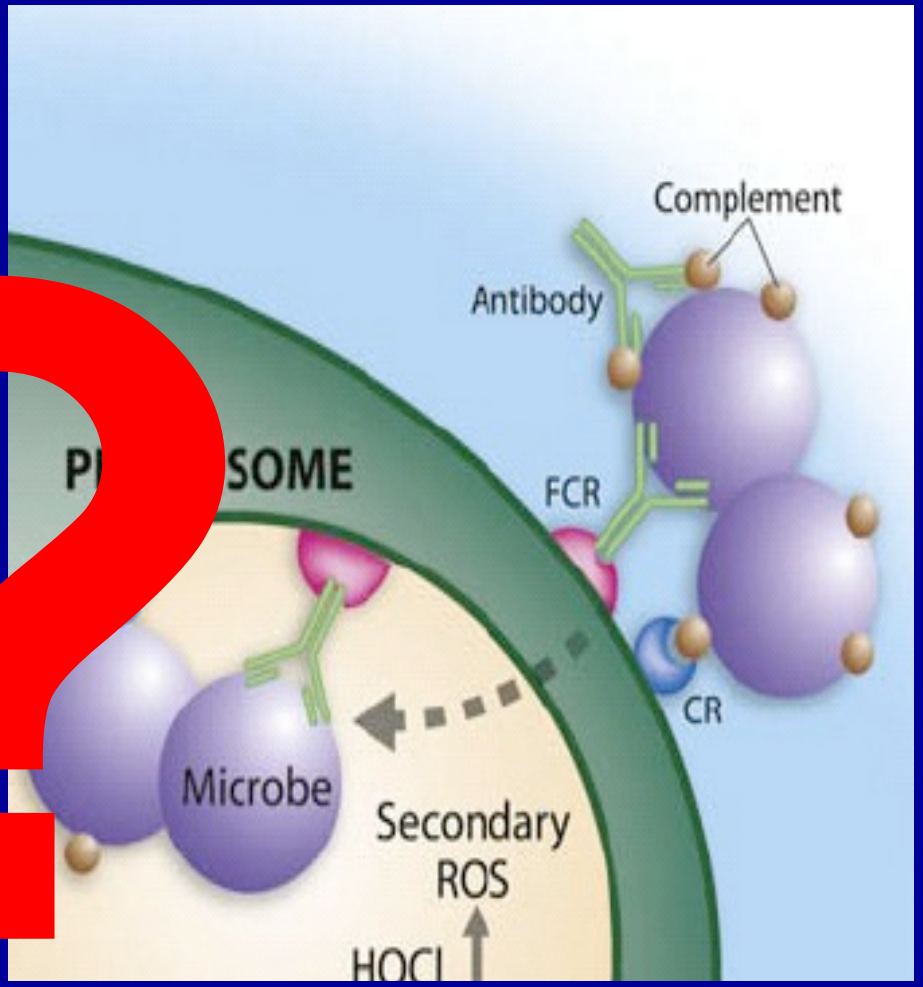
3) No Good Vaccine for *S. aureus*

KEY ASSUMPTION 1

Opsonophagocytosis is the Predominant Mechanism of Host Inflammatory Response to *S. aureus*

- Receptors for both Fc region of IgG and Complement Recep on Neutrophil
- Both IgG & C3 needed for opsonophagocytosis

Verbrugh J Immunol 1982; 129:1682-7



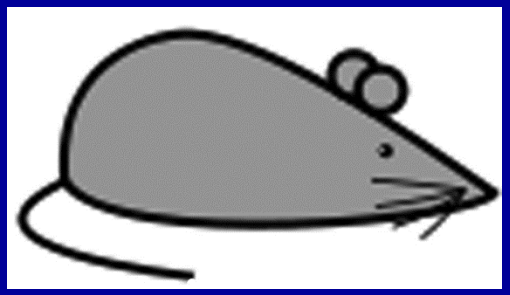
DeLeo et al Infect Dis Clin N Am 2009;23:17-34

Pre-Clinical Reliance on Opsonophagocytic Killing Assay in *S. aureus*

- *In vitro* evidence largely opsonophagocytic killing assay
- Efficacy for most candidates was based only on murine/rodent infection challenge
- Few used models mimicking clinical infection type
- Compound development:

  Murine sepsis to human infection trials

The Problem



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Genomic responses in mouse models poorly mimic human inflammatory diseases

Junhee Seok[a,1], H. Shaw Warren[b,1], Alex G. Cuenca[c,1], Michael N. Mindrinos[a], Henry V. Baker[c], Weihong Xu[a], Daniel R. Richards[d], Grace P. McDonald-Smith[e], Hong Gao[a], Laura Hennessy[f], Celeste C. Finnerty[g], Cecilia M. López[c], Shari Honari[f], Ernest E. Moore[h], Joseph P. Minei[i], Joseph Cuschieri[j], Paul E. Bankey[k], Jeffrey L. Johnson[h], Jason Sperry[l], Avery B. Nathens[m], Timothy R. Billiar[l], Michael A. West[n], Marc G. Jeschke[o], Matthew B. Klein[j], Richard L. Gamelli[p], Nicole S. Gibran[j], Bernard H. Brownstein[q], Carol Miller-Graziano[k], Steve E. Calvano[r], Philip H. Mason[e], J. Perren Cobb[s], Laurence G. Rahme[t], Stephen F. Lowry[r,2], Ronald V. Maier[j], Lyle L. Moldawer[c], David N. Herndon[g], Ronald W. Davis[a,3], Wenzhong Xiao[a,t,3], Ronald G. Tompkins[t,3], and the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program[4]

PNAS | February 26, 2013 | vol. 110 | no. 9 | 3507–3512

Immune Response to *S. aureus* in Humans, Mice, and Rabbits

	Animal		
Property	Human	Rabbit	Mouse
LPS lethality	0.013 µg per kg	500*–0.5‡ µg per kg	>80,000 µg per kg
α-toxin lethality	NA	0.005 µg per kg in 24 hours	>200,000 µg per kg
Superantigen lethality	0.0013 µg per kg	50*–0.05‡ µg per kg	Not lethal at 4×10^6 µg per kg
Similarity of cardiovascular physiology to that of humans	NA	Similar to humans	Not similar to humans
Similarity of fever response to that of humans	NA	Similar to humans	Not similar to humans

LPS, lipopolysaccharide; NA, not applicable. *Young adult (2–3 kg) rabbits. ‡8 month-old rabbits.

Salgado-Pabon Nature Reviews Microbiology 2014; 12:585-591.

Evidence for a Role of Th17 Cell-Mediated Immunity in *S. aureus* Immunity

- Humans with antibody also can have infection
  Fowler *JAMA* 2013
- Patients with defects in Th17 (STAT3 mutation) have high *S. aureus* infection rates Fischer *Immunol Cell Biol* 2008
- Transfer of Th17 cells, but not antibodies, protects mice from *S. aureus* infections Cho *JCI* 2010
- Protection with V710, Als3p, and ClfA conferred by Th17-mediated immunity and not antibodies
  Yeaman *PNAS* 2014; Joshi *Human Vaccin Immunother* 2012; Narita *Infect Immun* 2010; Lin *PLoS Pathogen* 2009

Did Th17 "Immune Priming" Cause the Multi-Organ system Failure Finding in Merck Trial?

Review

Is there a future for a *Staphylococcus aureus* vaccine?

Richard A. Proctor*

University of Wisconsin, Medical Microbiology/Immunology, 835 Asa Gray, Ann Arbor, MI 48105, United States

In summary, failures of previous staphylococcal vaccines most likely relates to our limited knowledge of the critical determinants of *S. aureus* immunity, the ability of *S. aureus* to remain pathogenic when only limited antigens are neutralized when armed with so many virulence factors, and the ability of *S. aureus* to thwart the immune system. The most recent information about the importance of Th17/IL-17 in protection from *S. aureus* infections provides hope that a "Staph Vaccine" can be developed. As a note of caution, the Th17/IL-17 arm of the immune system has implicated in autoimmune diseases; thus, subjects should be monitored for hyperimmune responses when receiving Th17/IL-17 targeted vaccines. Of course, another consideration will be to give up the notion of a single, broad spectrum "Staph Vaccine" and develop several vaccines targeted at different populations as *S. aureus* and different diseases. Finally, accepting goals less lofty than disease prevention and embracing goals of reduced severity or decreased colonization may make provide better opportunities for development of a successful vaccine.

Vaccine 30 (2012) 2921–2927

Human Vaccines & Immunotherapeutics 8:3, 336–346; March 2012; © 2012 Landes Bioscience

Immunization with *Staphylococcus aureus* iron regulated surface determinant B (IsdB) confers protection via Th17/IL17 pathway in a murine sepsis model

Amita Joshi,[1,*] Greg Pancari,[1] Leslie Cope,[1] Edward P. Bowman,[2] Daniel Cua,[2] Richard A. Proctor[3] and Tessie McNeely[1]

Vaccine-elicited CD4 T cells induce immunopathology after chronic LCMV infection

Pablo Penaloza-MacMaster,[1] Daniel L. Barber,[2] E. John Wherry,[3] Nicholas M. Provine,[1] Jeffrey E. Teigler,[1*] Lily Parenteau,[1] Stephen Blackmore,[1] Erica N. Borducchi,[1] Rafael A. Larocca,[1] Kathleen B. Yates,[4] Hao Shen,[3] W. Nicholas Haining,[4] Rami Sommerstein,[5] Daniel D. Pinschewer,[5,6] Rafi Ahmed,[7] Dan H. Barouch[1,8]†

CD4 T cells promote innate and adaptive immune responses, but how vaccine-elicited CD4 T cells contribute to immune protection remains unclear. We evaluated whether induction of virus-specific CD4 T cells by vaccination would protect mice against infection with chronic lymphocytic choriomeningitis virus (LCMV). Immunization with vaccines that selectively induced CD4 T cell responses resulted in catastrophic inflammation and mortality after challenge with a persistent strain of LCMV. Immunopathology required antigen-specific CD4 T cells and was associated with a cytokine storm, generalized inflammation, and multi-organ system failure. Virus-specific CD8 T cells or antibodies abrogated the pathology. These data demonstrate that vaccine-elicited CD4 T cells in the absence of effective antiviral immune responses can trigger lethal immunopathology.

Science 2015; 347: 278- 82.

The Journal of Infectious Diseases

MAJOR ARTICLE

Lethal CD4 T Cell Responses Induced by Vaccination Against *Staphylococcus aureus* Bacteremia

Hatice Karauzum,[1] Christian C. Haudenschild,[1] Ian N. Moore,[3] Mahta Mahmoudieh,[1] Daniel L. Barber,[2] and Sandip K. Datta[1]

[1]Bacterial Pathogenesis Unit and [2]T-Lymphocyte Biology Unit, Laboratory of Parasitic Diseases, and [3]Infectious Disease Pathogenesis Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

- Mice vaccinated with whole killed *S. aureus* who were subsequently infected with *S. aureus* bacteremia were significantly more likely to die than unvaccinated mice who were infected with *S. aureus* bacteremia
- Death due to CD4 T-cell dependent Interferon response
- Mortality prevented by inhibiting Interferon response
- *Results identify the potential for vaccination to induce pathological immune responses, and they have implications for recent vaccine failures and the design of future staphylococcal vaccines*

2017;215:1231–9

Why do the Trials Fail?
Three Possibilities

1) Good Vaccine, Bad Trial

2) Good Vaccine, Bad Assumption

3) No Good Vaccine for *S. aureus*

Development Terminated

Active	Staphvax (Nabi)
	V710 (Merck)
	PF-06290510 (Pfizer)
Passive	Altastaph
	Arsanis
	Aurexis
	Aurograb
	Pagibaximab
	Veronate

Remaining Candidates

Sponsor	Antigens	Phase	Possible Limitations
NovaDigm	Als3	P I	Single antigen
NABI/GSK protein	PVL, Alpha Toxin	P I	Secreted protein targets
GSK (Belgium)	CP5, CP8, Alpha Toxin, ClfA	P I	3 of 4 are “recycled” targets, 1 is secreted target
GSK (Novartis)	Tetravalent, All protein	P I	Ability of protein to elicit robust opsonophagocytic antibodies
Vaccine Research Intl	Whole Cell	P I	Variable immunogenicity of whole Cell

REMAINING CANDIDATES
Active Vaccines

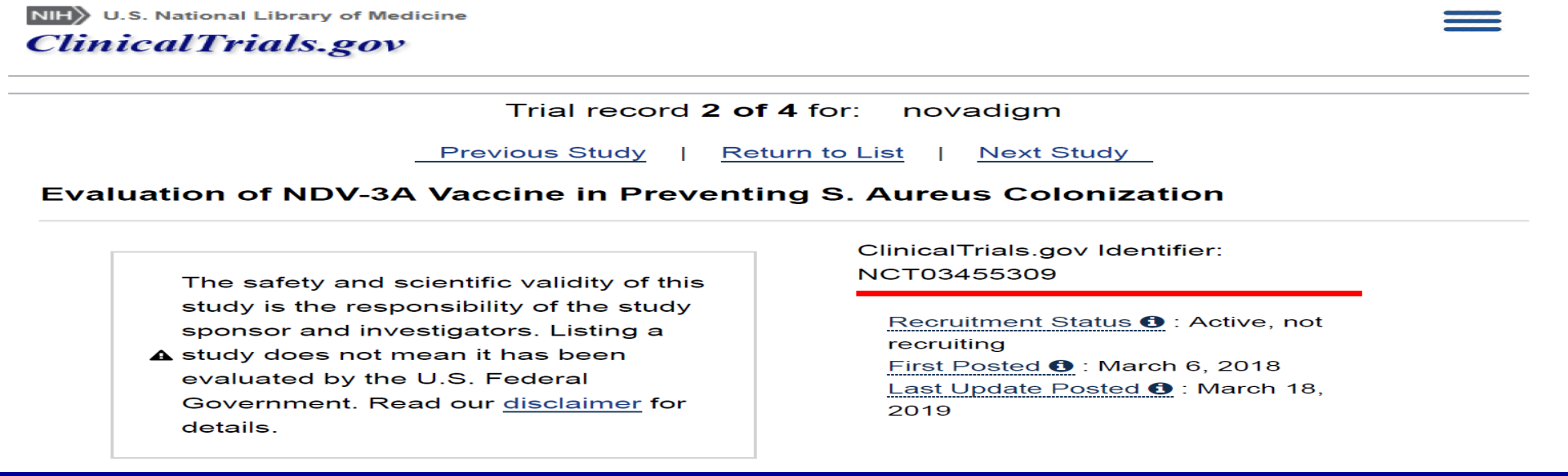
Novadigm

Mechanisms of NDV-3 vaccine efficacy in MRSA skin versus invasive infection

Michael R. Yeaman[a,b,c,d,1], Scott G. Filler[a,b,d], Siyang Chaili[b,c,d], Kevin Barr[d], Huiyuan Wang[b,c,d], Deborah Kupferwasser[b,c,d], John P. Hennessey Jr.[e], Yue Fu[a,b,d], Clint S. Schmidt[e], John E. Edwards Jr.[a,b,d], Yan Q. Xiong[a,b,d], and Ashraf S. Ibrahim[a,b,d]

- ↓ abscess progression, dissemination to kidney.
- ↑ CD3+ T-cell neutrophil infiltration and IL-17A, IL-22, and host defense peptide expression.
- IL-22 necessary protection against skin infection.
- IL-17A and IL-22 required for protection against hematogenous dissemination

Yeaman *PNAS* 2014



- Double-blind Phase 2 RCT of 382 Military Recruits
- **1˚ Endpoint:** Change in *S. aureus* Nasal Colonization by d56
- **2˚ Endpoint:** SSTI rates

Novartis

Vaccine composition formulated with a novel TLR7-dependent adjuvant induces high and broad protection against *Staphylococcus aureus*

Fabio Bagnoli[a], Maria Rita Fontana[a], Elisabetta Soldaini[a], Ravi P. N. Mishra[a], Luigi Fiaschi[a], Elena Cartocci[a], Vincenzo Nardi-Dei[a], Paolo Ruggiero[a], Sarah Nosari[a], Maria Grazia De Falco[a], Giuseppe Lofano[a], Sara Marchi[a], Bruno Galletti[a], Paolo Mariotti[a], Marta Bacconi[a], Antonina Torre[a], Silvia Maccari[a], Maria Scarselli[a], C. Daniela Rinaudo[a], Naoko Inoshima[b], Silvana Savino[a], Elena Mori[a], Silvia Rossi-Paccani[a], Barbara Baudner[a], Michele Pallaoro[a], Erwin Swennen[a], Roberto Petracca[a], Cecilia Brettoni[a], Sabrina Liberatori[a], Nathalie Norais[a], Elisabetta Monaci[a], Juliane Bubeck Wardenburg[b], Olaf Schneewind[c], Derek T. O'Hagan[a], Nicholas M. Valiante[a], Giuliano Bensi[a], Sylvie Bertholet[a], Ennio De Gregorio[a], Rino Rappuoli[a,1], and Guido Grandi[a,1]

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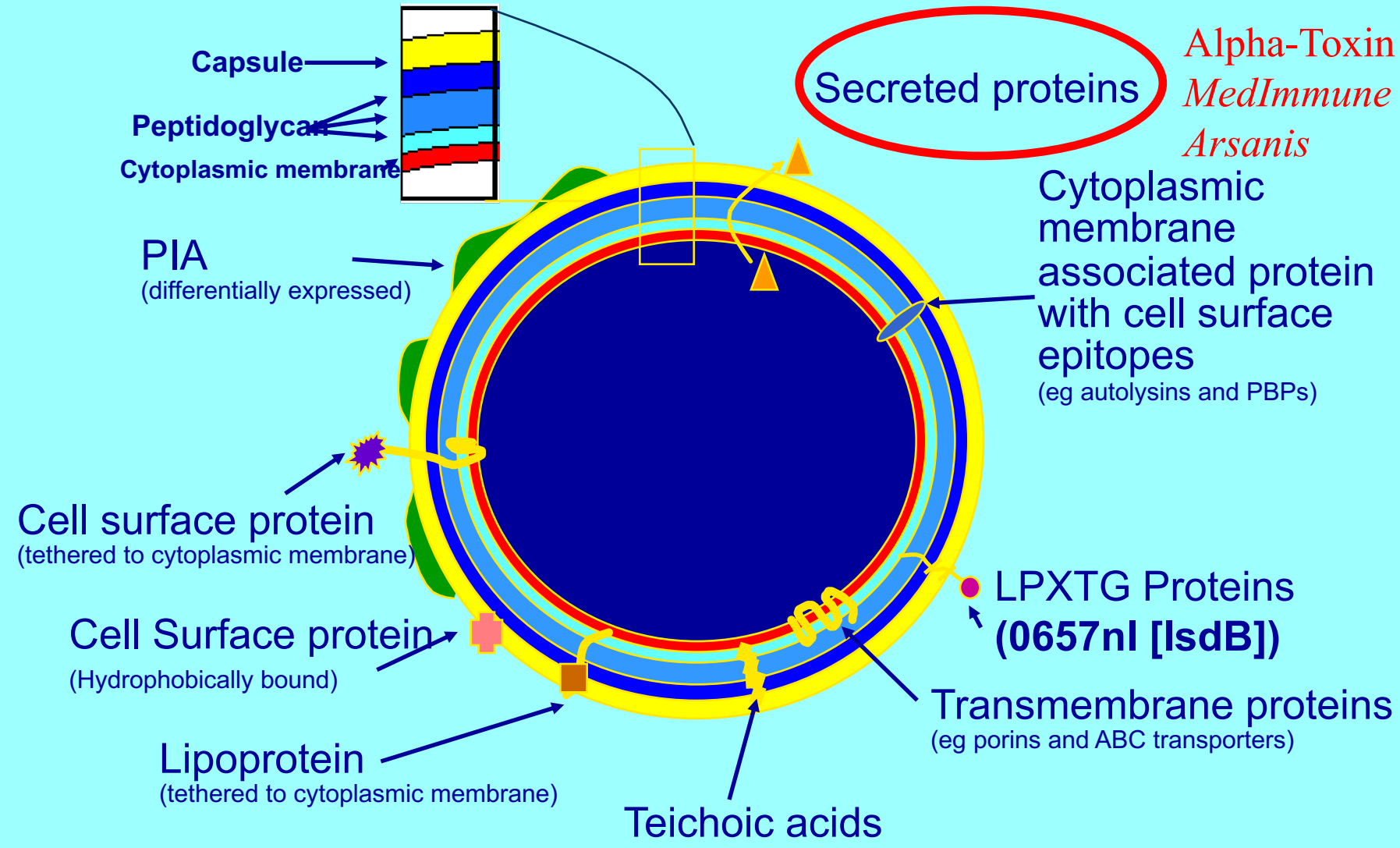
New Passive Immunotherapeutics for Prevention

Monoclonal Antibodies that Target α Toxin

MEDI4893
ASN100

Vaccine Target Antigens for Staphylococci



MEDI4893
MedImmune

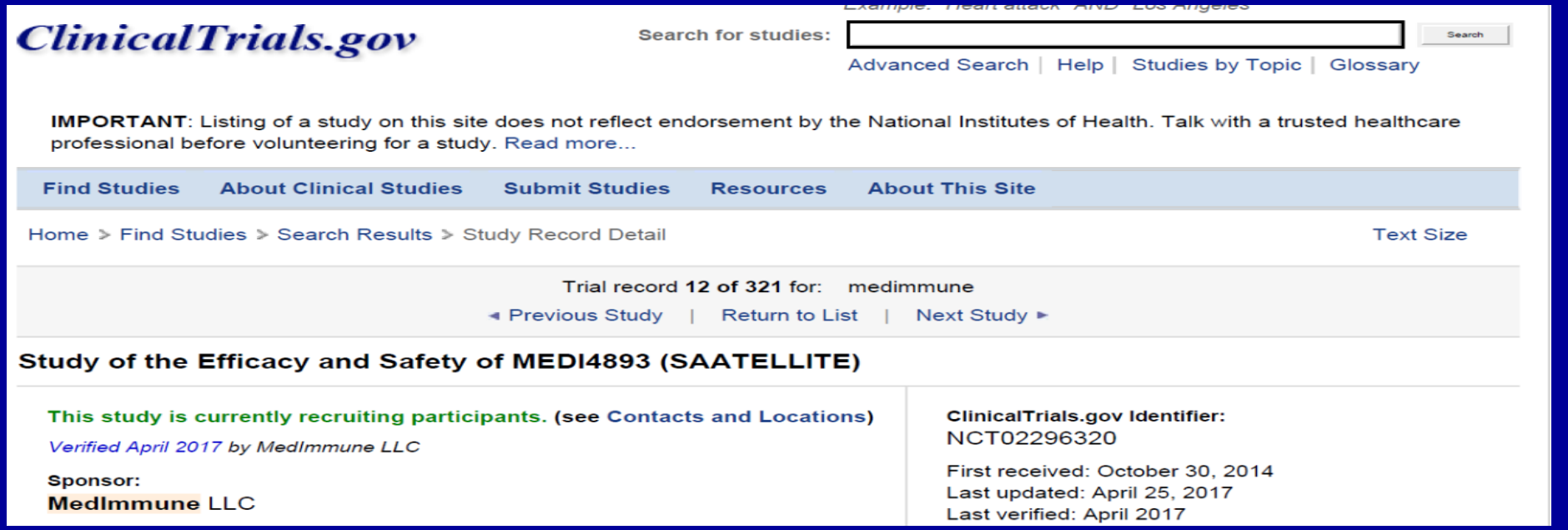
Assessment of an Anti-Alpha-Toxin Monoclonal Antibody for Prevention and Treatment of *Staphylococcus aureus*-Induced Pneumonia

L. Hua,[a] J. J. Hilliard,[a] Y. Shi,[a] C. Tkaczyk,[a] L. I. Cheng,[b] X. Yu,[b] V. Datta,[b] S. Ren,[b] H. Feng,[c] R. Zinsou,[a] A. Keller,[a] T. O'Day,[d] Q. Du,[b] L. Cheng,[c] M. Damschroder,[c] G. Robbie,[b] J. Suzich,[a] C. K. Stover,[a] B. R. Sellman[a]

Antimicrobial Agents and Chemotherapy | February 2014 Volume 58 Number 2

Anti-α toxin Mabs Associated with

- *Increased survival in pneumonia model*
- *Minimal lung inflammatory response*
- *Lower proinflammatory cytokines*
- *Better oxygenation (lower pCO2)*
- *Additive or synergistic when combined with antibiotics*



- Phase II, Randomized, Double-Blind, Dose-ranging study of MEDI4893 in Mechanically Ventilated Adults
- Enrolling: Europe (IMI)
- 1° endpoint: *S. aureus* pneumonia through D31
- Inclusion: *S. aureus*- colonized
- Exclusion: No antistaphylococcal antibiotics

ASN100
Arsanis

Five birds, one stone: Neutralization of α-hemolysin and 4 bi-component leukocidins of *Staphylococcus aureus* with a single human monoclonal antibody

Harald Rouha[1], Adriana Badarau[1], Zehra C Visram[1], Michael B Battles[2,†], Bianka Prinz[2], Zoltán Magyarics[1], Gábor Nagy[1], Irina Mirkina[1], Lukas Stulik[1], Manuel Zerbs[1], Michaela Jägerhofer[1], Barbara Maierhofer[1], Astrid Teubenbacher[1], Ivana Dolezilkova[1], Karin Gross[1], Srijib Banerjee[1,†], Gerhild Zauner[1], Stefan Malafa[1], Jakub Zmajkovic[1], Sabine Maier[1], Robert Mabry[2,†], Eric Krauland[2], K Dane Wittrup[2,3], Tillman U Gerngross[1,2,4], and Eszter Nagy[1,*]

- Single Monoclonal Antibody that recognizes conformational epitope shared by Alpha hemolysin and f-components of Gamma-hemolysin (HlgAB and HlgCB), LukED and LukSD.
- Amino acids forming the common epitope are conserved, lyse human phagocytes, epithelial cells, and RBC
- Superior ability to protect against cytolytic effects of secreted *S. aureus* toxins vs Alpha toxin Antibodies alone

mAbs 7:1, 243–254; January/February 2015

- Phase II, Randomized, Double-Blind study of ASN100 in Prevention of *S. aureus* Pneumonia in Heavily Colonized Ventilated Adults
- Enroll: goal 354
- 1° endpoint: *S. aureus* pneumonia through D22
- Inclusion: 3+ or 4+ *S. aureus*- colonized
- Exclusion: Heavy colonization with Gram-negative bacteria

29th ECCMID
Amsterdam, Netherlands
13 – 16 April 2019
The congress of ESCMID

L0011 Results of a Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Safety and Efficacy of a Single Dose of the Monoclonal Antibody Combination ASN100 for the Prevention of *Staphylococcus aureus* Pneumonia in Endotracheal Heavily Colonized, Mechanically Ventilated Subjects

Zoltan Magyarics*[1], Karin Provost[2], Nimrod Adi[3], Tomasz Czarnik[4], Khatuna Japaridze[5], Nikoloz Kartsivadze[6], Mikhail Kirov[7], Ed Campanaro[8], Matthew Goodwin[8], Lori Muir[8], Marin Kollef[9], Chris Stevens[8]

L0013 Efficacy and Safety Profile of Suvratoxumab, a Novel Anti-Staphylococcus aureus Monoclonal Antibody: Results of the SAATELLITE Study in Mechanically Ventilated Intensive Care Unit Patients

Bruno François*[1], Miguel Garcia Sanchez[2], Philippe Eggimann[3], Pierre-Francois Dequin[4], Pierre-Francois Laterre[5], Vincent Huberlant[6], Dolores Escudero[7], Thierry Boulain[8], Cédric Bretonnière[9], Jerome Pugin[10], José Trenado Álvarez[11], Ana Catalina Padilla[1], S. Omar Ali[12], Kathryn Shoemaker[12], Alexey Ruzin[12], Vadryn Pierre[12], Yuling Wu[12], Julie Vignaud[1], Susan Colbert[12], Terramika Bellamy[12], Filip Dubovsky[12], Hasan S. Jafri[12]

	Arsanis **ASN100**	**MedImmune** **Suvratoxumab**
Design	Double-blind, placebo-controlled Superiority design Phase II of prevention of *S. aureus* pneumonia in mechanically ventilated patients	
Study Population	Mechanically ventilated ICU pts "heavily colonized"	Mechanically ventilated ICU pts PCR + colonized
Test of Cure	22 days post study drug	30 days post study drug
Endpoint	*S. aureus* Pneumonia	*S. aureus* pneumonia *Per blind adjudication committee*
	152 patients from 35 sites	196 patients from European sites
Results	28.2% RRR *-6.6% Drug vs. 9.2% Placebo*	31.9% RRR *-17.7% Drug vs. 26% Placebo*
	Terminated for futility by DRC	P = 0.166 *- 2-sided significance p< 0.1*

Conclusions

- Universally unsuccessful despite
  - *Multiple antigens*
  - *Multiple strategies: therapeutic, preventive*
  - *Multiple patient populations*
- Innovative New Immunotherapeutics in trials
- Future candidates need
  - *>1 Antigen*
  - *Efficacy in > 1 non-murine/rodent model*
  - *Close safety monitoring*
- The field won't survive another *S. aureus* vaccine trial failure

Funding

2R01-AI068804

RO1-HL119648

U01-AI124319

2K24-AI093969

NO1-AI90023

UM1-AI104681