Novel glycoconjugate vaccines based on rationally designed synthetic carbohydrate antigens

Stewart Campbell
Ancora Pharmaceuticals

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Ancora Pharmaceuticals Inc.

World leaders in synthetic carbohydrate chemistry company.

Vaccine Technology IV
Albufeira, Portugal

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Ancora Pharmaceuticals: Overview

• Founded on the groundbreaking carbohydrate synthesis technology from Prof. Dr. Peter Seeberger (Max Planck)

• Demonstrated track record in producing commercially relevant synthetic carbohydrates across the glycobiology spectrum

• Primary R&D focus: glycoconjugate vaccines for prevention of nosocomial and opportunistic infections

• Business focus: build value through partnered and proprietary programs

• World class team of managers and advisors

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Management and Advisors

- **Richard Hoffman**, J.D., M.B.A. CEO; 20+ years in biopharmaceutical corporate and business development (Abgenix, Ablexis)

- **Stewart Campbell**, Ph.D. Vice President - Research & Development; 18 years in biopharmaceutical therapeutic development; 16 years carbohydrate chemistry expertise.

- **Obadiah Plante**, Ph.D. Co-founder, Senior Director - Vaccine Discovery; 15 years carbohydrate chemistry expertise.

- **Professor Peter Seeberger**, Ph.D. Director, Scientific Founder; World leader in carbohydrate chemistry and glycobiology; Elected Director of the Max Planck Institute

- **Barry Buckland**, Ph.D. Director and Scientific Advisor; ex-VP Bioprocess for Merck Vaccines; 30+ years vaccine & biologic product development

- **Florian Schodel**, M.D. Scientific Advisor; ex-VP Clinical Development for Merck Vaccines; 20+ years vaccine research and clinical development

- **George M. Siber**, M.D. Scientific Advisor; ex-CSO for Wyeth Vaccines; 30+ years vaccine research & development

- **Bruce Forrest**, M.D., M.B.A. Corporate and Scientific Advisor; ex-SVP Vaccine Research & Development for Wyeth Vaccines (Pfizer); 20+ years vaccine research and clinical development

- **Rahul Singhvi**, Sc.D., MBA. Director; former President/CEO of Novavax; former scientist at Merck Vaccines.

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Glycoconjugate Vaccines – Proven Products, Persistent Barriers

• Commercially Validated Approach:
  • Pneumococcus
    – Prevnar®
    – Synflorix®
  • Meningococcus
    – Menactra®
    – Menveo®
  • Hib:
    – Comvax®
    – HibTITER®
    – Hiberix®

  – Why only 3 pathogens addressed so far?

• Major Barrier:
  – Limited access to defined carbohydrate material
Carbohydrate Production: State-of-the-Art BioProcessing Can Be Limiting

Biological material source

Isolated material

Purified average structures

Bacterial surface

Target antigen

Impurity

Bioprocesses yield average structures (mixtures) which can impede every stage:

- Discovery (POC)
- Development (CTM)
- Commercial (Mfg)
Chemical Synthesis Platform Unlocks Carbohydrate Space

Ancora synthesis technology platform produces defined structures

Building block technology  Assembly capabilities  Processing methodologies

No limitation to structure or material access – Ancora has completed every target structure to date

Opens entire glycobiology application space

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Demonstrated Production of Diverse, Complex Mammalian Carbohydrate Structures

N-/O-linked structures (biotherapeutics)

Highly branched structures (biotherapeutics)

Complex adhesion structures (inflammation)

Heparan sulfates (coagulation, targeting)

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Demonstrated Production of Diverse, Complex Pathogen Carbohydrate Structures

Bacterial

Meningitis B

Parasitic

Burkholderia

Group A Strep

Leishmania

Lipid A

Malaria toxin

Fungal

C. albicans β-glucan

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Ancora Platform Provides Access to Virtually Any Complex Carbohydrate Structure

Example: Leishmania LOS

Design and optimize for desired biological profile
Attributes of Synthetic Carbohydrate Antigen Approach

Vaccine discovery

- Unattainable structures
- New targets
- "Core" structures
- Antigen "Med Chem"
- Optimization
- Epitope mapping
- Conjugation control
- Presentation
- Loading

Vaccine development

- Large scale, well-defined antigens
- Regulatory
- Manufacturing
- Safety

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Synthetic Antigens Provide Excellent Conjugation Control

**Candida β-glucan conjugates**

- Purified
  - Lam-CRM197
  - Curd-CRM197
  - 17mer-CRM197
  - 15mer-CRM197
  - CRM197

**Group A Strep PS conjugates**

- Synthetic

Bromuro et al. Vaccine 28 (2010) 2615 (Novartis Vaccines)

Kabanova et al. Vaccine 29 (2010) 104 (Novartis Vaccines)
Ancora Platform Capabilities: Scalable to Support Discovery Through Early Clinical Trials

Building blocks

Assembled structures

Multi-kg scale

100 g - kg scale

Final, active material

100 g scale (clinical program scale)

Cost Competitive

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# Ancora Vaccine Portfolio: Focus on Nosocomial Infections

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Staphylococcus Vaccine Program: Antigen Optimization via “Med Chem”
**Staphylococcus Vaccine Opportunity**

- **Target Populations and Medical Need:**
  - **Incidence:**
    - > 1.7 MM nosocomial infections annually
    - CoNS and *S. aureus* in top five
  - **At-risk populations:**
    - Elective Cardiovascular Surgery – 7 MM procedures
    - Orthopedic Surgery – > 1 MM procedures
    - End-Stage Renal Disease – 600,000 patients
  - High drug resistance (MRSA), high mortality rate (20% of HAI)
  - High economic burden: >$30,000/ICU patient

- **Staphylococcus as a Target:**
  - Gram positive, biofilm producing bacterium
  - Usually encapsulated (Types 5, 8, 336 account for most human infections)
  - Complex infection life-cycle → multi-valent approach likely required

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Staphylococcal PIA/PNAG: Major Biofilm Component and Virulence Factor

- dPNAG provide physical interface between bacterium and biofilm
- Human anti-dPNAG antibody levels correlated with *in vitro* OPA activity

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Precedent for PNAG as a Target Antigen: Purified PS & Purified DT-Conjugate

Purified PNAG Mixtures (Pier et al.)

DT-Conjugates of purified PNAG Mixtures (Pier et al.)

Partial deacetylation, Conjugation

Antigen size, functional group pattern, conjugation UNCONTROLLED

Immunogenic; active in vitro and in vivo

Deacetylation required for immunoprotection → optimum pattern UNCLEAR

Pier group *Science* 284 (1999) 1523
Pier group *Infect Immun* 73 (2005) 6752

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dPNAG Antigen Chemical Space: Defining the Problem

Vast chemical space defined $\rightarrow > 10^{30}$ permutations in DP x Degree alone

Requires directed empirical and rational approach

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Precedent for PNAG as a Target Antigen: Synthetic TT-Conjugates

Synthetic PNAG/dPNAG fragments covering two extremes: fully N-acetylated, fully N-deacetylated

Showed synthetic dPNAG conjugate provides passive immunoprotection

Acetylation patterns, pattern repeats not addressed

Protection after active immunization not demonstrated

Pier, Nifantiev groups *Infect Immun* 78 (2010) 764

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dPNAG Chemical Space: State-of-the Art versus Ancora

Ancora platform:
- Grants access to the ENTIRE dPNAG chemical space
- Enables systematic and rational optimization of antigen structure
Ancora *Staphylococcus* Vaccine Program: Synthetic Antigens with Defined Patterns

**Defined Synthetic Antigen Library**

- **Defined Pattern 1**
  - Ag 1
  - Ag 2
  - Ag 3

- **Defined Pattern 2**
  - Ag 4
  - Ag 5
  - Ag 6

- **Defined Pattern 3**
  - Ag 7
  - Ag 8
  - Ag 9

**Specific Conjugation Site**

- R = Patterned H, Ac

```
O
HO- O
HO- O
NHR  HO- O
O
LINKER
```

- **Carrier**

**“Medicinal Chemistry” approach to identifying best Ag**

Rational antigen library design $\rightarrow$ head-to-head testing

Antigen size, functional group pattern, conjugation are EXACT
**Staphylococcus Vaccine Program:**
Functional Proof-of-Concept

*In vitro* opsonophagocytosis assay (OPA):
Complement-mediated killing by human PMN’s

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**In vitro**: Antisera selectively bind bacteria (WBE)

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In Vivo Proof-of-Concept: Murine Lethal Challenge Model

- S. aureus Newman inoculum: $5.6 \times 10^8$ (LD$_{50}$)
- CD1 outbred mice (n = 10 per group)
- Schedule: 3 x 10 ug @ 11-day intervals, rest 14d, i.v. challenge

• Trend: dPNAG-KLH conjugates showed better protection vs. controls
• PNAG-KLH no better than controls

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Staphylococcus Vaccine Program: Competing Antibodies Phenomenon

Lee, Pier and coworkers characterized neutralizing effect of combined anti-CP and anti-dPNAG Abs both in vitro (OPA) and in vivo (bacteremia, skin abscess models)

- Identified the same phenomenon in sera from bacteremia patients
- Traced mechanism to direct binding of respective variable regions to each other


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New dPNAG Antigen Design Criteria

- ≤ 50% N-acetylation degree
- de-N-acetylated residues spaced by two intervening residues were disallowed
- ≤ 2 de-N-acetylated residues allowed in positions complementary to the CP ManAcA residues in an entire sequence (length dependent)
- ≤ 3 consecutive N-acetylated residues allowed
- Minimize overall length

Desired output: Improved antigen devoid of anti-CP interference properties
Moraxella Vaccine Program: Targeting Novel “Core Structures”
Moraxella catarrhalis Vaccine Program

**Significant unmet medical need**
- COPD: Over 2 million infections annually (2\textsuperscript{nd})
- *Otitis media*: Over 30% of acute *otitis media* cases (3\textsuperscript{rd})
- A leading cause of LRTIs in vulnerable populations
- Widespread drug resistance

**Target Antigen Overview:**
- Gram negative lipo-oligosaccharide (LOS) class
- Critical for survival and virulence
- A, B, and C serotypes: 95% of human infections
- Validated target *in vitro* and *in vivo*

**Goal:** Identify antigen structures and substructures cross-protective across all major MXLA strains


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Moraxella Vaccine Program: Antigen Design

Chemistry provides unique systematic approach to core structures

Core

α-chain

β-chain

Serotype A

Serotype B

Serotype C

Lipid A

Antigen library synthesized and conjugated

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**Moraxella Vaccine Program:**

**Cross Reactivity ELISA of Rabbit Antisera**

**Background**

Threshold

**OD (net)**

*Pre-immune 1:25000 1:125000 1:625000*

Analogs 4 and 5 show significant, broad cross-reactivity
Moraxella Vaccine Program: Serum Bactericidal Assay (SBA) Data

SBA titers ≤ 1:250 for parent and cross-reactive Ag’s (n = 4 mean shown)

ELISA cross-reactivity translates into SBA activity
Pseudomonas Vaccine Program: Targeting Biofilm & “Hybrid Core” Structures
**Pseudomonas Vaccine Program**

**P. aeruginosa**

**Significant Market Opportunity:**
- 2\textsuperscript{nd} leading cause of ventilator associated pneumonia
- 3\textsuperscript{rd} leading cause of hospital-acquired pneumonia
- CF Patients: Most common lung infection, leading cause of morbidity and mortality
- Antibiotic resistance reaching critical level

**Target Antigen Overview:**
- 3 potential targets based on conserved nature, virulence role and colonization
- Alginate biofilm (1) expressed in chronic mucoid infections
- O-antigens (2) expressed in acute non-mucoid infections
- LOS core (3) expressed in all infection stages

**Pseucomonas Vaccine Program:**
Automated Synthesis of Alginate Antigen

**Design and Chemistry Approach**
- Series of β-mannuronic acids of varying length
- Assembled in a day from a one building block (1) using Ancora’s automated synthesizer
- Functional group for subsequent conjugation
- Evaluation in progress

- Collaboration with Leiden University

Ancora's automated carbohydrate synthesizer

Ancora Summary

• Diverse, broadly applicable carbohydrate synthesis platform

• Demonstrated track record of generating relevant synthetic carbohydrate antigens (defined, homogeneous)

• Internal focus on glycoconjugate vaccines for the prevention of nosocomial and other infections

• Excellent team of experienced managers and advisors

• Business strategy: partner after demonstration of preclinical POC
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