Non Confidential Introduction to ThermoVax®

Proprietary Thermo-Stabilization Platform for Vaccines Outside the Cold Chain

October 2016

ThermoVax® Technology

A proprietary vaccine formulation platform imparting enhanced thermostability

- Stability at high temperatures (>40ºC)
  - Extremely labile subunit *stable* for at least 1 year at 40ºC
  - Demonstrated stability for at least 16 weeks at 70ºC
- Delivers long-term stabilization of labile antigen-adjuvant combinations
- Primary proof of concept work with aluminum adjuvanted vaccines
- Maintains native structure
- Applicable to many types of commercial vaccines
  - Polysaccharide conjugates, VLPs, recombinant subunit proteins and peptides
  - Complex vaccines utilizing “secondary adjuvants”
  - Combination as well as multivalent vaccines

Avoiding the Cold Chain: The Need for Thermostable Vaccines

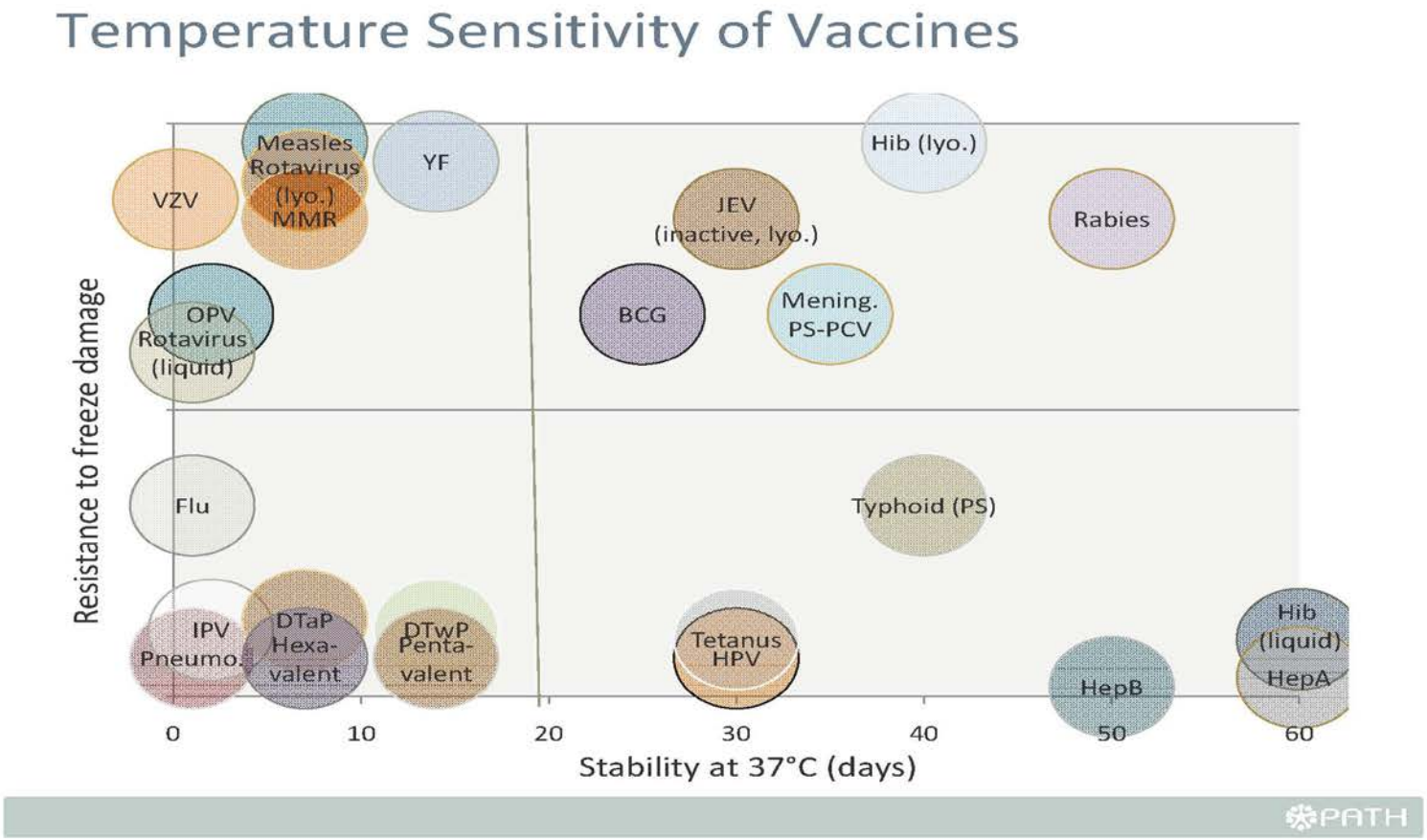
- Total vaccine market exceeded $21B in 2010[1]
- $20.6B or 98% of all vaccines require shipment through cold chain[2]
- Maintaining cold chain increases the cost of vaccination by 14–20%[3]
  - Establishing & maintaining cold chain requires significant investment (>$200M/yr)
  - Major logistic & capacity constraint from manufacturer to physician/pharmacy
- Potency loss & spoilage due to breaks in the cold chain can be substantial
  - Leads to ineffective protection and safety concerns
  - 50% losses in emerging nations – GAVI
  - 10% losses in established markets – Australian MoH
  - 75-100% of vaccines experience “temp excursions” during shipment[4]
- Recent DHHS report entitled “Vaccines for Children Program: Vulnerabilities in Vaccine Management,” demonstrates the need for thermostable vaccines
  - Undetected cold chain variations put recipients at risk of exposure to impotent vaccines[5]
- **Thermostable vaccines represent a major commercial & public health opportunity in both emerging and established markets**

1) Vaccines Market Report, Kalorama, 2010
2) Biopharma Cold Chain Sourcebook 2010
3) WHO Estimate
4) Mattias et al, Vaccine (2007)
5) DHHS Report 2012

Thermostable Vaccines: Value Proposition

- Value Proposition – Established Markets
  - Drive Market Share with a differentiated product
  - Thermostable vaccines preferred by Physician offices and pharmacies
    - Decreased need for refrigerator/freezer space and monitoring
    - Less waste/returns from questionable vaccine
  - Decreased logistics costs – eliminate cold chain logistics
  - Potential to extend IP position
  - Potential opportunity for biosimilars to differentiate
- Value Proposition – Emerging Markets
  - Improved Access – Number 1 challenge facing public health authorities
    - Eliminate cold chain logistics
  - Improved outcomes – maximize impact in public health
    - Less risk of inactivated vaccine
  - Potential to formulate multivalent and/or combination vaccines
  - Decreased public health spend – lower logistic costs

Temperature Sensitivity of Marketed Vaccines



Source: PATH

Vaccines Outside the Cold Chain

- All of the components of a vaccine are subjected to some form of degrading force (water, heat, light)
  - Complex protein or protein-carbohydrate antigens are susceptible to inactivation
  - Adjuvants and vehicles are also vulnerable
- Special need for long-term stability exceeding labeling for most vaccines impedes implementation of EPI vaccination programs for a spectrum of vaccine products

Vaccine Instability

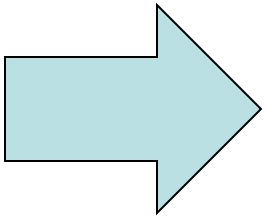
Principal pathways of recombinant subunit protein vaccine instability *occurring in water*

Chemical

- Oxidation (methionine)
- Deamidation (asn/gln)
- Disulfide exchange (inter- or intra-chain)
- Hydrolysis/peptide fragmentation

Physical

- Dimerization/multimerization
- Aggregation
- Conformational changes
  - Molten globule
  - Incompletely disordered
  - Random coil



Loss of native structure
Loss of effectiveness/potency
Incorrect or altered antigen processing
    Loss of linear determinants
    Loss of conformational determinants
Decreased binding and dissociation of antigen and adjuvant
Heightened thermal instability

Proof of Concept Studies

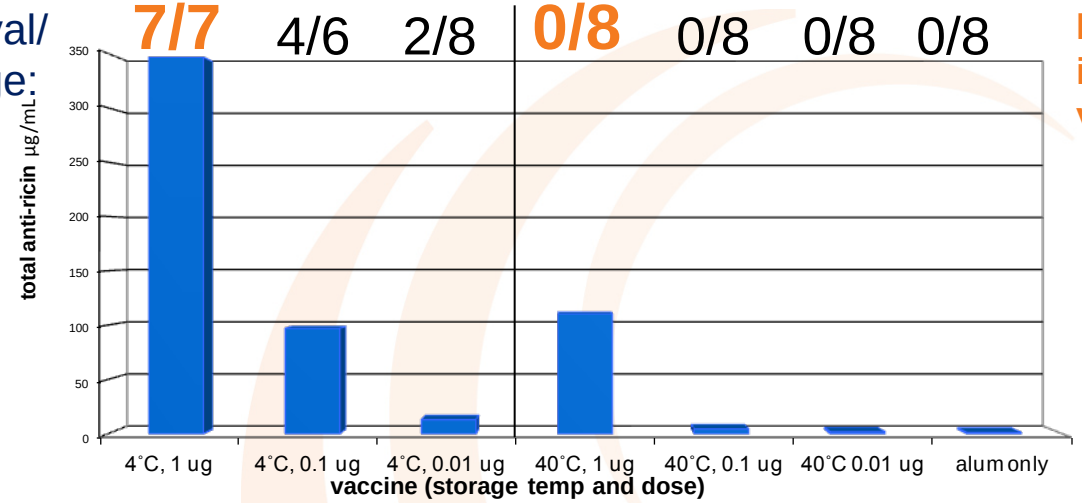
ThermoVax® applied to the following vaccines:

- Ricin vaccine (RiVax™)
  - Based on ricin A-chain protein antigen containing 2 point mutations to minimize toxicity
  - Liquid vaccine extremely labile at room temperature
  - Uses an aluminum adjuvant
- Anthrax vaccine
  - Based on Domininant Negative Inhibitor (DNI) of recombinant protective antigen (rPA)
  - Can incorporates both an aluminum adjuvant and a secondary adjuvant (TLR-4 agonist)
  - Liquid vaccine loses efficacy quickly under ambient conditions
- Human papillomavirus (HPV) vaccine
  - Marketed as a VLP vaccine (Cervarix®, Gardasil®) – converted to a subunit vaccine with enhanced thermostability

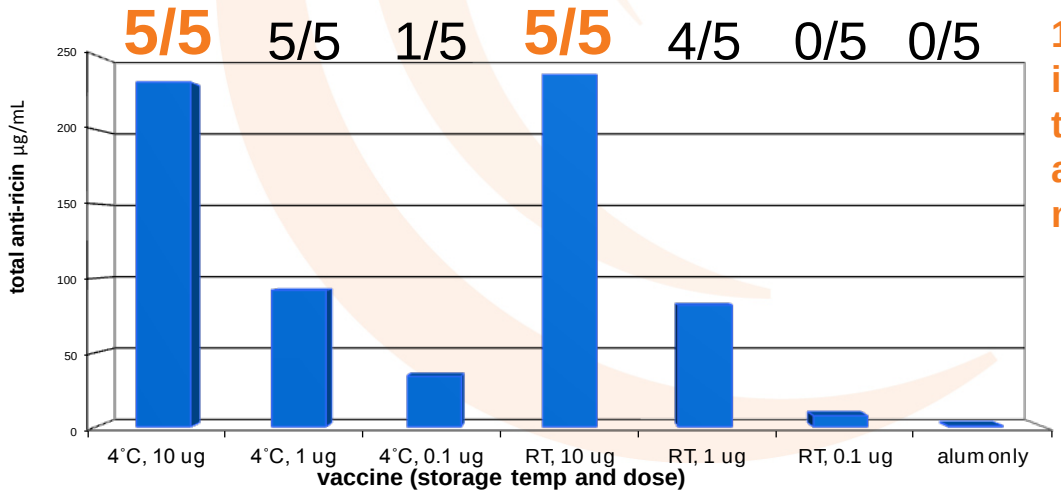
RiVax™ Animal Immunogenicity

Liquid adsorbed RiVax™ loses potency at 40°C while Thermostable RiVax™ retains efficacy

Mouse Survival/ ricin challenge:



No mice survived after immunization with liquid vaccine at 40˚C

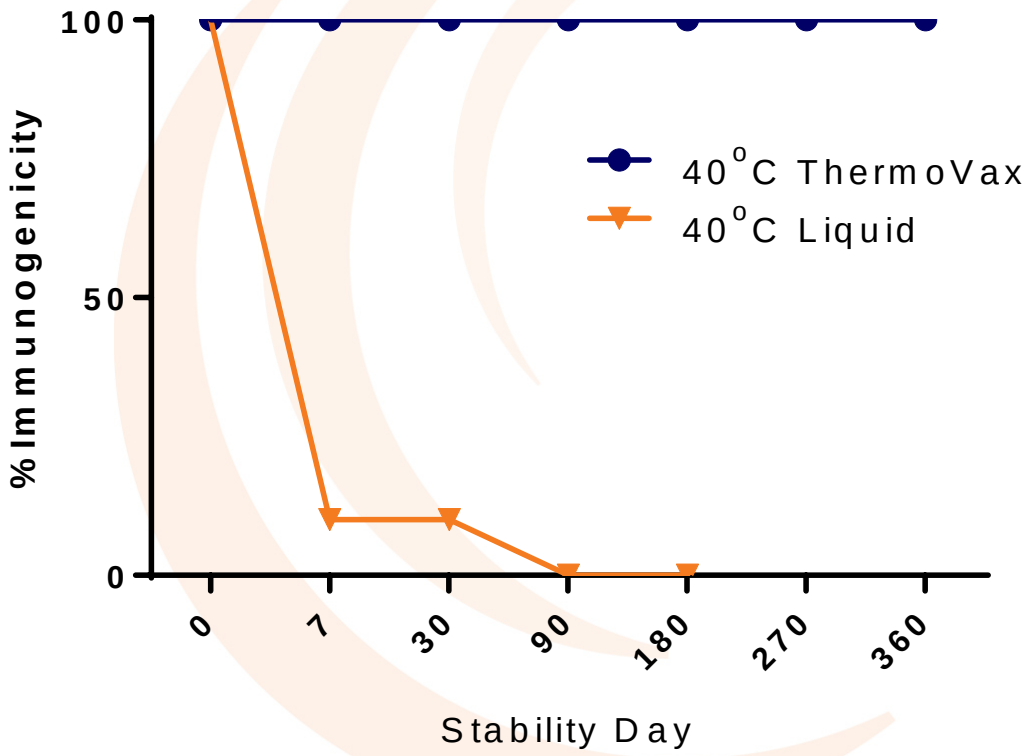


100% survival after immunization with thermostable vaccine stored at room temperature for 12 months

Note: **these experiments were not performed in parallel and therefore antibody levels are not directly comparable between the 2 graphs**

ThermoVax® Proof of Concept - RiVax™

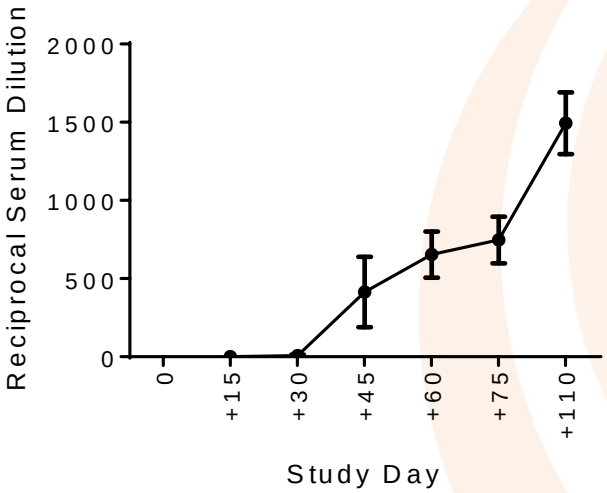
Vaccine effective at inducing antibodies in mice after storage for 1 year at 40°C when stabilized with ThermoVax®



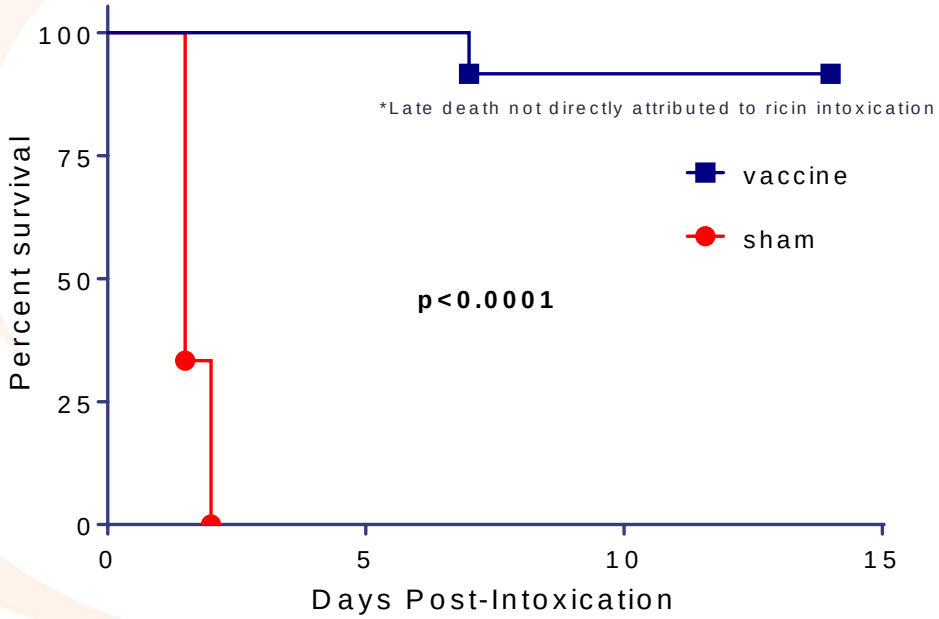
Thermostable RiVax™ Provides 100% Protection

Vaccination protects against lethal ricin challenge in NHPs

Neutralizing Antibodies Elicited after 2 Vaccinations



Vaccinated Animals are Protected from a Lethal Aerosol Challenge



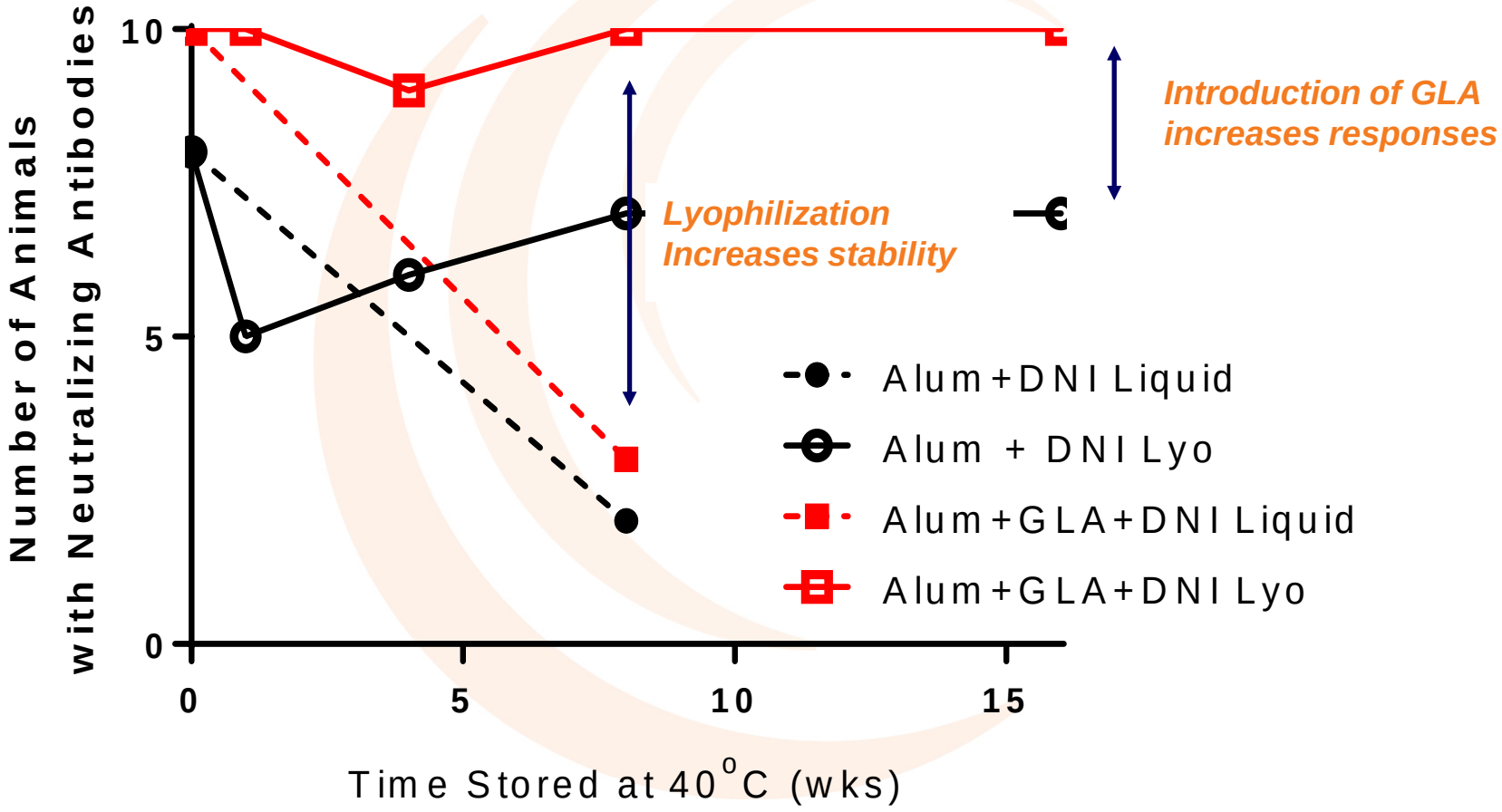
Vaccination and Aerosol Challenge

- Vaccinated animals were administered RiVax-TR (thermostabilized ricin vaccine) on Days 0, 30 and 60. Neutralizing antibodies were determined on Study Day 15 (2 weeks after initial vaccination), 30 (prior to vaccination), 45 (15 days after second vaccination), 60 (prior to third vaccination), 75 (15 days after third vaccination), and 110 (prior to challenge). Control animals received matched injections (sham-vaccinated).
- On Day 110, each animal was challenged with 3-5xLD50 of aerosolized ricin. Control animals died within 40 hours.

*C. Roy et al, .PNAS, 2015, 112(12): 3782-87

Thermostable Anthrax Vaccine - Immunogenicity

Lyophilization prevents loss of neutralizing antibodies
Demonstrated compatibility with secondary adjuvant (GLA)

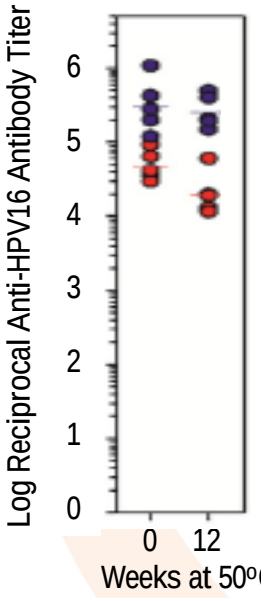


*K. Hassett et al. J. Pharm Sci., 2015, 104(2): 627-39

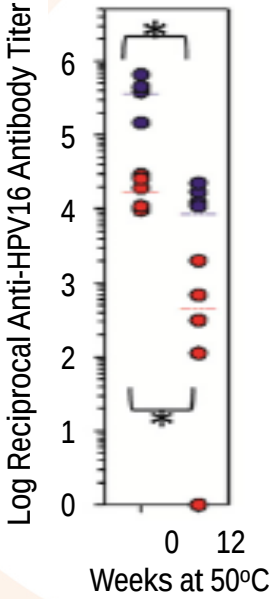
Application to a Commercial Indication

*Conversion to a subunit vaccine **maintains immunogenicity**, **increases thermostability** (no cold chain required) and **simplifies manufacturing***

Capsomere+ Alum + GLA



Cervarix®



Vaccination and Aerosol Challenge

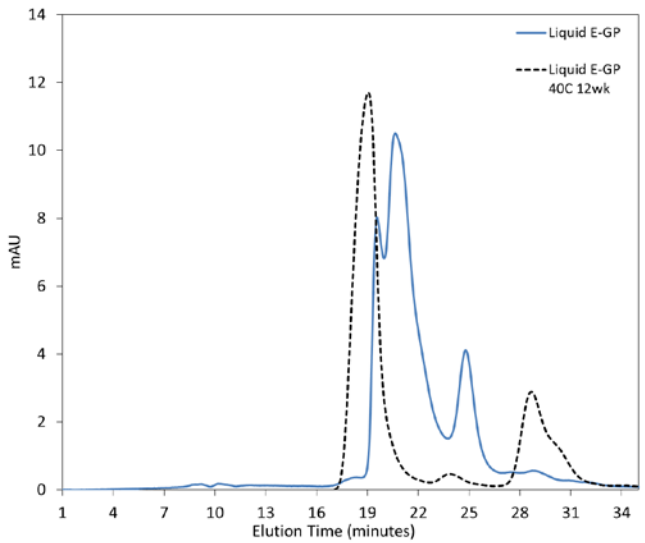
- HPV Capsomere and Cervarix® were stored at 50°C for 12 weeks. Immunogenicity was tested before after storage. On Days 0 and 21, Female Balb/c mice were administered HPV16L1 ("capsomere"; 5 μg) or Cervavix ® (4 μg) intramuscularly. Antibody responses were determined after 1 dose on Day 21 (red circles) and after 2 doses on Day 36 (blue circles).

*K. Hassett et al. European Journal of Pharmaceutics and Biopharmaceutics, 2015, http://dx.doi.org/10.1016/j.ejpb.2015.05.009

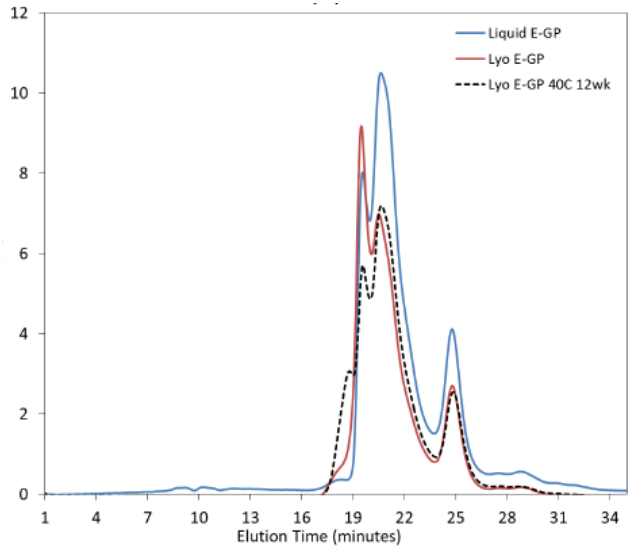
Stabilizes Ebola GP Protein

Increases the Physical Stability of the Ebola GP Protein Antigen

Liquid Formulation: Aggregation over Time



Lyophilized Formulation: Unchanged over Time



Protein Structure Studies

- Ebola GP protein has a pronounced tendency to aggregate. Monomeric and high and low molecular weight protein species were monitored using size-exclusion HPLC and a TSKgel G3000SW$_{XL}$ column
- Liquid EBOV GP formulations incubated for 12 weeks at 40°C had loss of monomer and increased levels of high and low molecular weight species.
- Lyophilized EBOV GP formulations incubated for 12 weeks at 40°C were relatively unchanged.

*K. Hassett et al. European Journal of Pharmaceutics and Biopharmaceutics, 2015, http://dx.doi.org/10.1016/j.ejpb.2015.05.009

Seeking Collaboration

Soligenix is actively seeking partnership opportunities for its ThermoVax® Platform

- Research Collaboration
  - Feasibility Study with an option to License
  - Utilizing innovator's antigen/vaccine, Soligenix will formulate and validate thermostable properties
- ThermoVax® available for License

ThermoVax® References

- Recent Posters
  - Chisholm, C.F., Kang, T.K., Lehrer, A., Donini, O, Randolph, T.W. Thermostable Lyophilized Ebola Vaccine Formulations. Poster presentation at the 2016 Workshop on Protein Aggregation and Immunogenicity. August 2-4, 2016. http://www.soligenix.com/wp-content/uploads/poster-ebola_vaccine_2016-chisholm.pdf
  - Leffel, E., Roy, C.J., Brey, R.N., Donini, O. Thermostable Subunit Vaccine Results in Protective Immunity in Rhesus Macaques in an Inhalational Ricin Model. Poster Presentation at 2015 ASM Biodefense and Emerging Diseases Research Meeting. February 9-11, 2015. http://soligenix.stage.pingsite.com/pdfs/soligenix_rivax_asm_biodef.pdf
- Recent Papers:
  - Hassett, K.J., Meinerz N.M., Semmelmann F., Cousins M.C., Garcea, R.L, Randolph, T.W. 2015. Development of a highly thermostable, adjuvanted human papillomavirus vaccine. Eur. J. Pharm. Biopharm. http://dx.doi.org/10.1016/j.ejpb.2015.05.009
  - Roy, C.J., Brey, R.N., Mantis, N.J., Mapes K., Pop, I.V., Pop, L.M., Ruback, S., Zilleen, S.Z., Doyle-Meyers, L., Vinet-Oliphant, H.S., Didier, P.J., Vitetta,, E.S. 2015. Thermostable ricin vaccine protests rhesus macaques against aerosolized ricin: Epitope-specific neutralizing antibodies correlate with protection. PNAS 112(12): 3782-87. http://www.pnas.org/content/112/12/3782.full.pdf
  - Vance, D.J., Rong, Y., Brey, R.N., Mantis, N.J. 2015. Combination of two candidate subunit vaccine antigens elicits protective immunity to ricin and anthrax toxin in mice. Vaccine 33(3): 417-21.
  - Hassett K.J., Vance D.J., Jain, N.K., Sahni, N., Rabia, L.A., Cousins, M.C., Joshi, S. Volkin, D.B., Middaugh, C.R., Mantis, N.J., Carpenter, J.F., Randolph, T.W., 2015. Glassy-state stabilitization of a dominant negative inhibitor anthrax vaccine containing aluminum hydroxide and glycopyranoside lipid adjuvants. J. Pharm. Sci 104(2): 627-39.

THANK YOU

SOLIGENIX

For additional information on partnering with Soligenix, please contact us at your convenience:

Christopher J Schaber, PhD
President & CEO
Soligenix, Inc.
Ph: 609 538 8200