Highly efficacious influenza vaccination using αGal carbohydrate modification

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A wholly-owned subsidiary of
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Disclaimers

- Speaker has interest in the company represented herein (stocks and stock options)

- *These slides accompany an oral presentation by BioProtection Systems, a wholly-owned subsidiary of NewLink Genetics Corporation, which contains forward-looking statements. The Company's actual results may differ materially from those suggested here. Additional information concerning factors that could cause such a difference is contained in the Company's Quarterly Report on Form 10-Q for the fiscal quarter ended June 30, 2014 and other prior and subsequent regulatory filings.*

NewLink Genetics Corporation

- Located in Ames, Iowa
- Incorporated in 1999
- IPO in 2011, traded on NASDAQ
- ~115 employees (and growing)
- Core competency in immunology and oncology
- Multiple oncology products in Phase 1, 2 and 3 clinical trials
  - Cancer immunotherapies and immunomodulators
  - Curative intent active Cellular Cancer Immunolotherapy
  - Small molecule inhibitors of immunosuppressive pathways

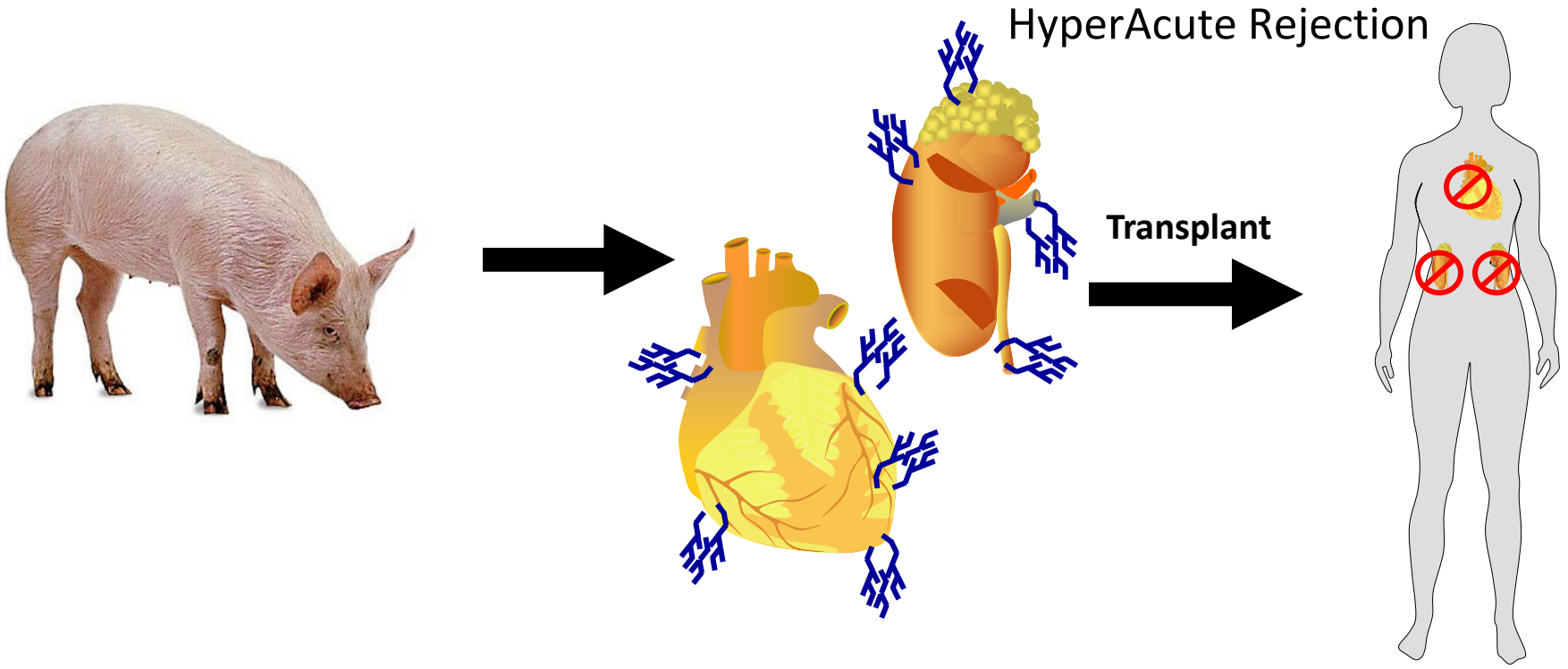
BioProtection Systems Corp

- Located Ames, IA
- 11 Full-time employees
- Vaccine emphasis
  - Biodefense and pandemic targets
- Acquired by NewLink Genetics 2011

αGal and HyperAcute™

- αGal = carbohydrate on many proteins and lipids
- Humans, apes and old world monkeys do not have αGal
- Anti-αGal antibodies very abundant in serum and mucosa (normal flora have αGal or related carbohydrates)
- αGal = Key antigen for hyperacute rejection of xenotransplants

Xenotransplantation → Hyperacute rejection



Anti-αGal antibodies are responsible for hyperacute rejection of xenotransplants

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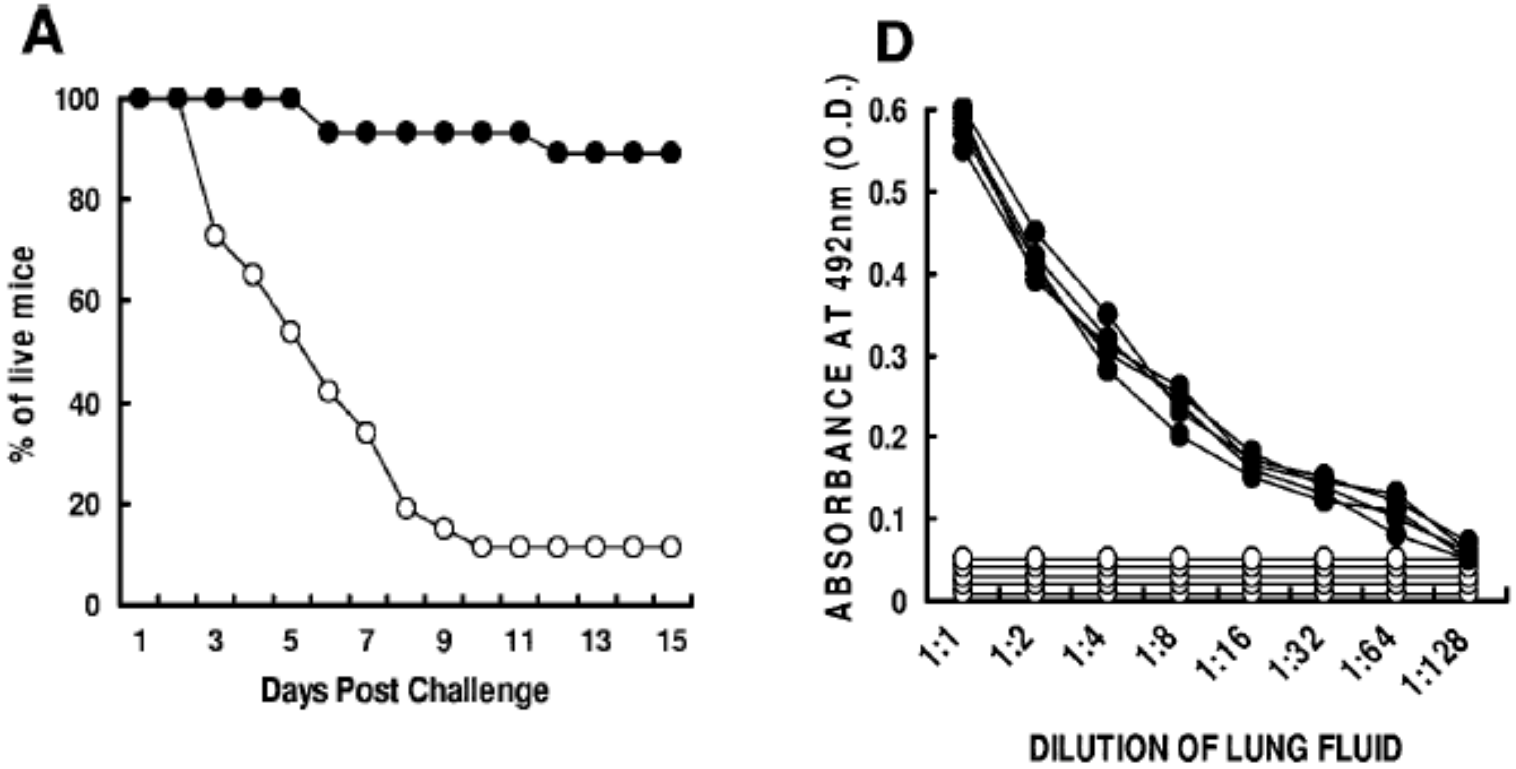
HyperAcute Vaccines

- Theory: loss of αGal in humans and old world primates → protection of human beings from zoonotic infections
- Birds do not have αGal, therefore we are susceptible to bird viruses
- Hypothesis: Use of HyperAcute technology will increase the immunogenicity of vaccines
- NewLink in Phase III trials with pancreatic cancer immunotherapy with HyperAcute technology

Uri Galili – αGal in Influenza Vaccine

H1N1 PR8 whole virus vaccine: J. Virol. 81:9131



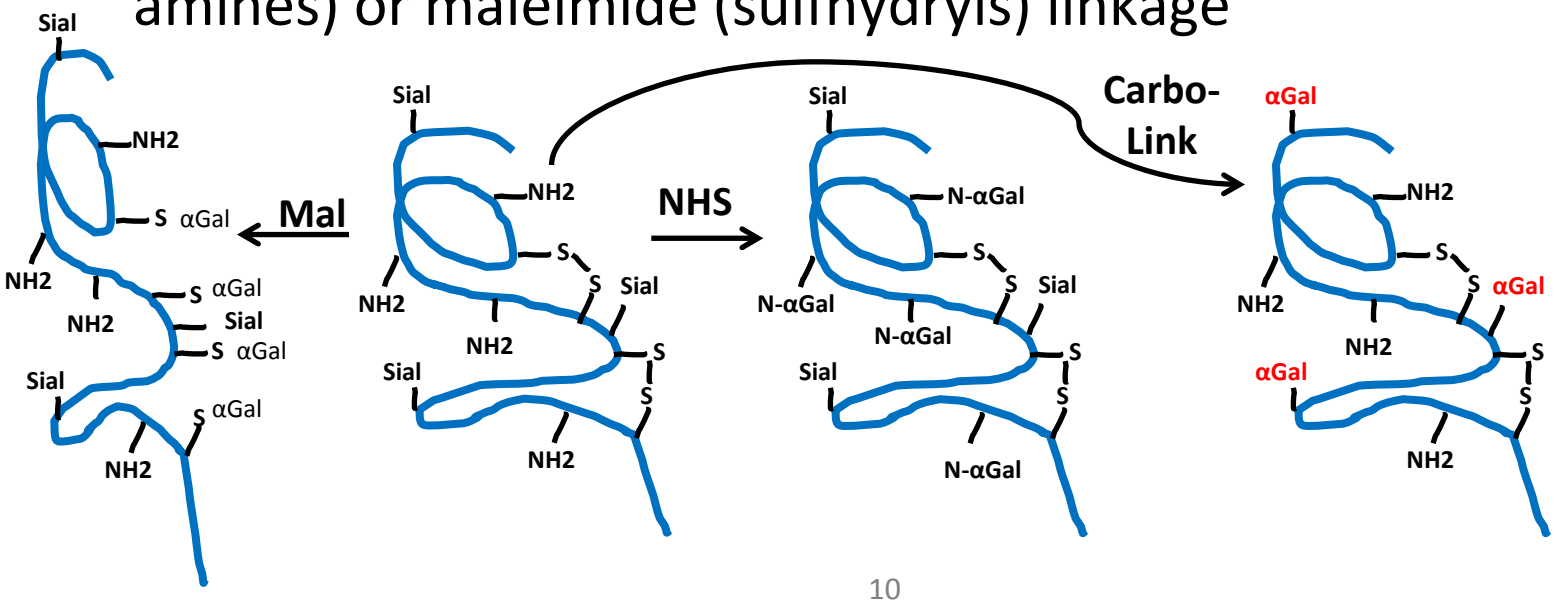
Conclusion: αGal significantly increases vaccine efficacy.

Concerns

- Galili's experiments were done with adjuvant and large amounts of HA (1 µg/injection)
- The αGal labeling was done using the α1,3-galactosyltransferase enzyme *in vitro*
- Both the enzyme and the substrate are difficult to make and expensive
- Can we come up with a better way to achieve the αGal response?

Novel linker modification of proteins

- Utilizes the naturally occurring N-linked carbohydrates on proteins made in mammals
- Does not alter the structure of the protein
- Novel formulation
- Very different from typical NHS (N-hydroxysuccinimide; primary amines) or maleimide (sulfhydryls) linkage

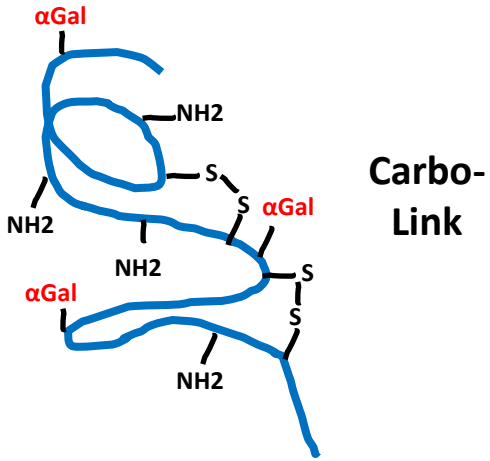


Vaccine formulation

- Based upon H1N1 (A/Puerto Rico/8/34), H5N1 and H7N9
- Virus-like particle (VLP) vaccines:
  - Cloned the influenza HA, NA and M1 protein
  - Expressed in 293 cells by transient transfection
  - Purified by differential sedimentation on gradients
- Recombinant protein vaccines
  - Trimer or oligomer HA proteins expressed in mammalian cells

Carbo-Link modification of vaccines

- VLPs or recombinant protein vaccine isolated from 293 cells
- Modified with either control linker (contained everything but αGal) or Carbo-Link
- Injected 100 ng (or amount indicated) of HA equivalent into mice (2 times, 4 weeks apart)
- Mice were bled 2 weeks after the second vaccination



Carbo-Link

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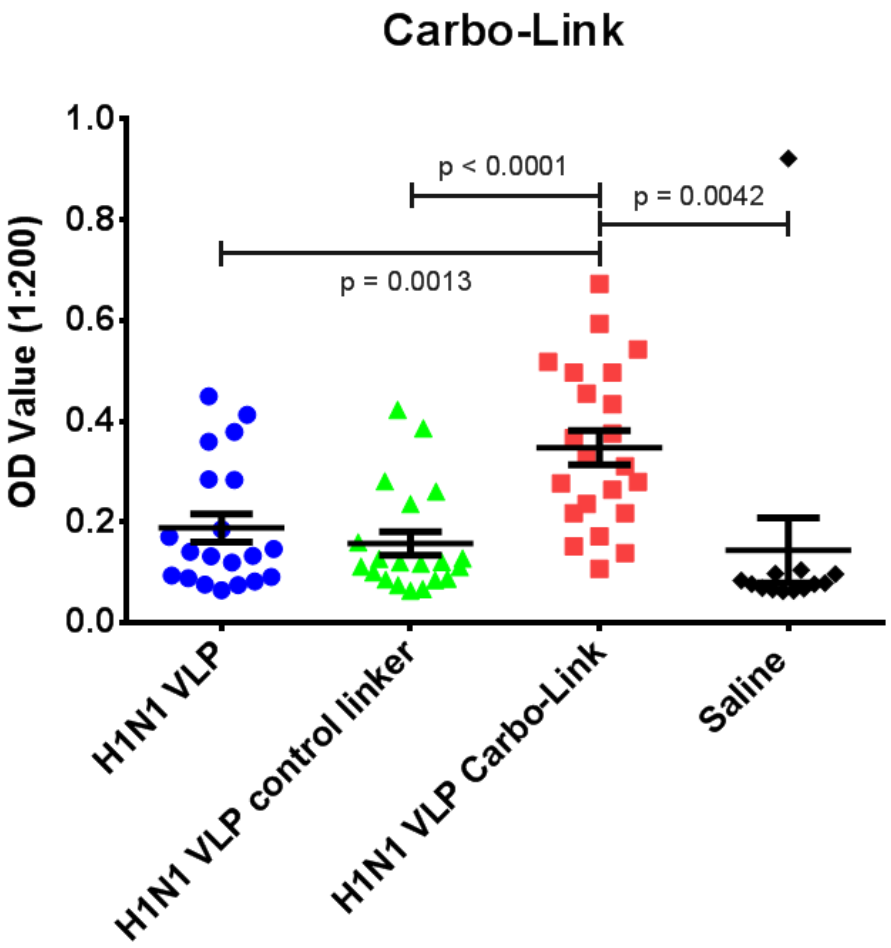
Carbo-Link, H1N1 VLPs



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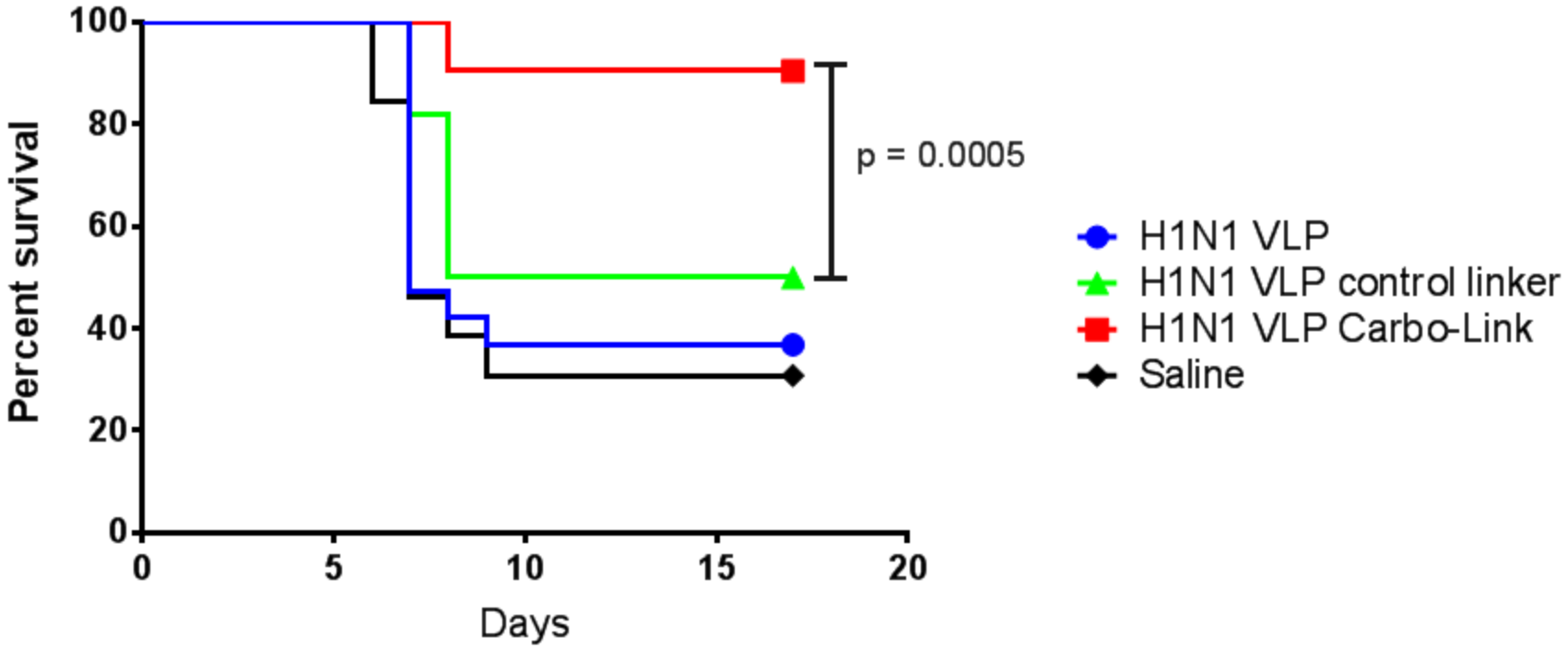
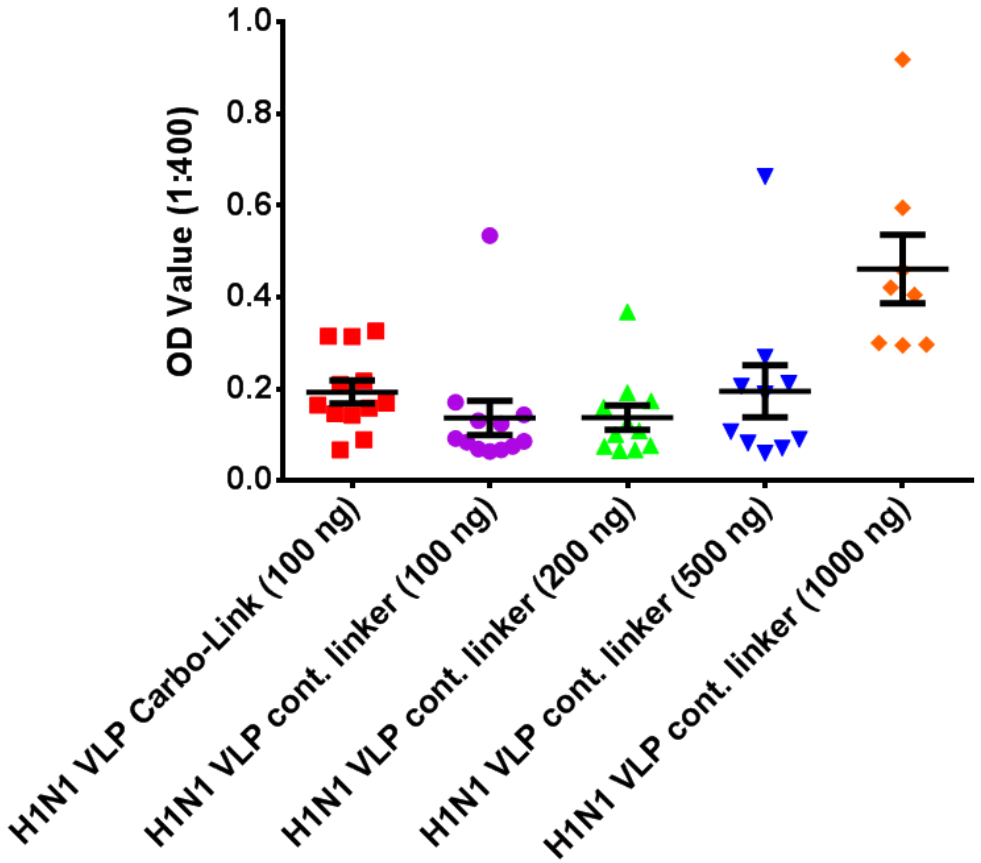
Carbo-Link H1N1 VLP Survival



Carbo-Link H1N1 VLP Dose-Response



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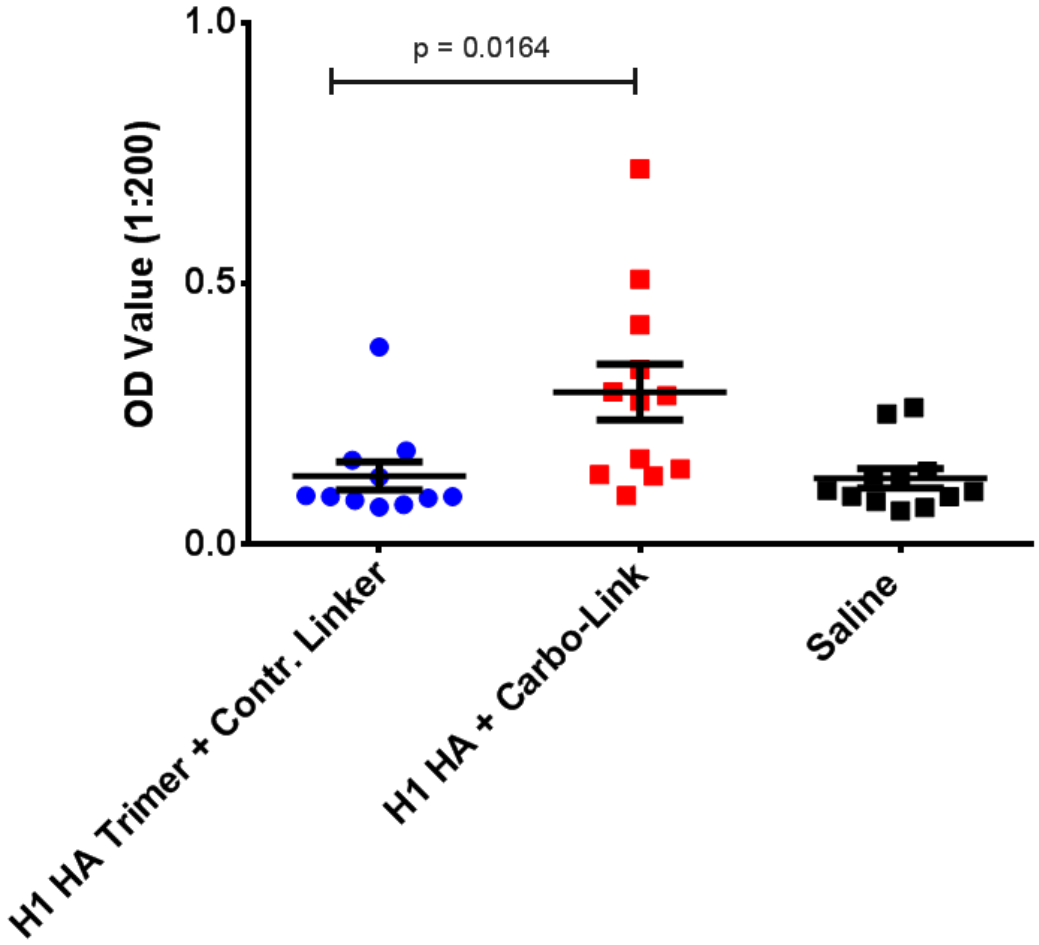
Carbo-Link H1 recombinant protein vaccine



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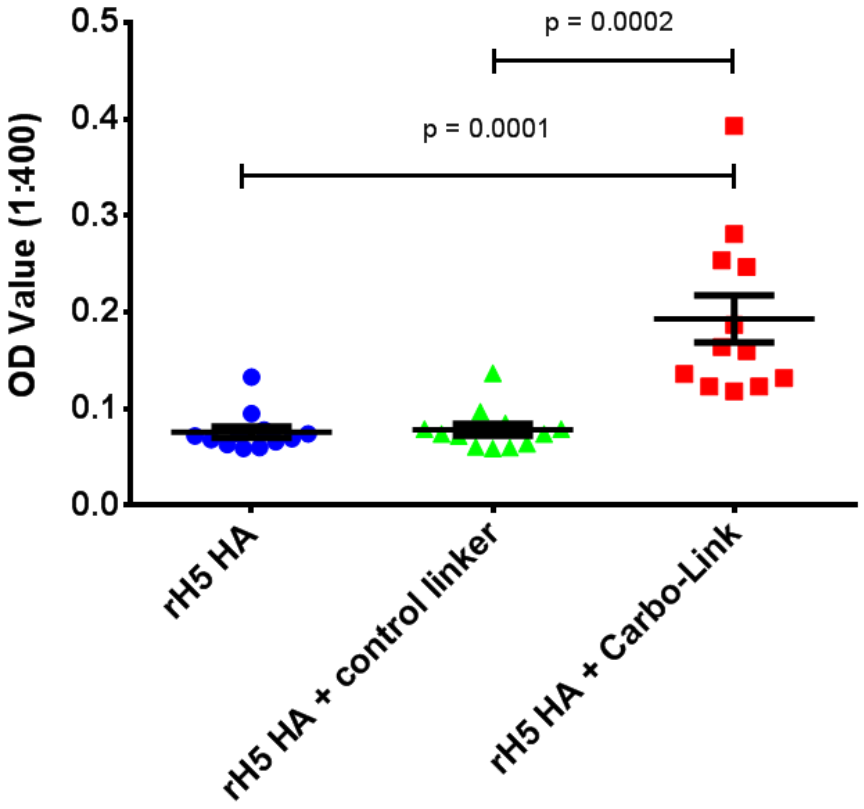
Carbo-Link recombinant H5 vaccine



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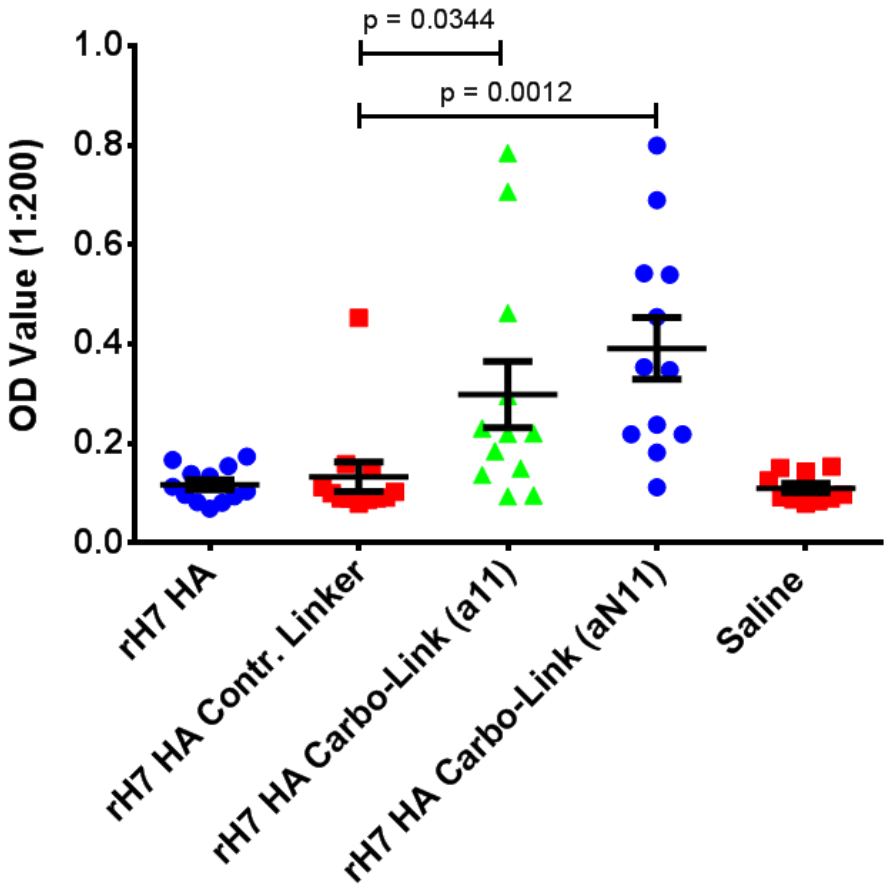
Carbo-Link recombinant H7 vaccine



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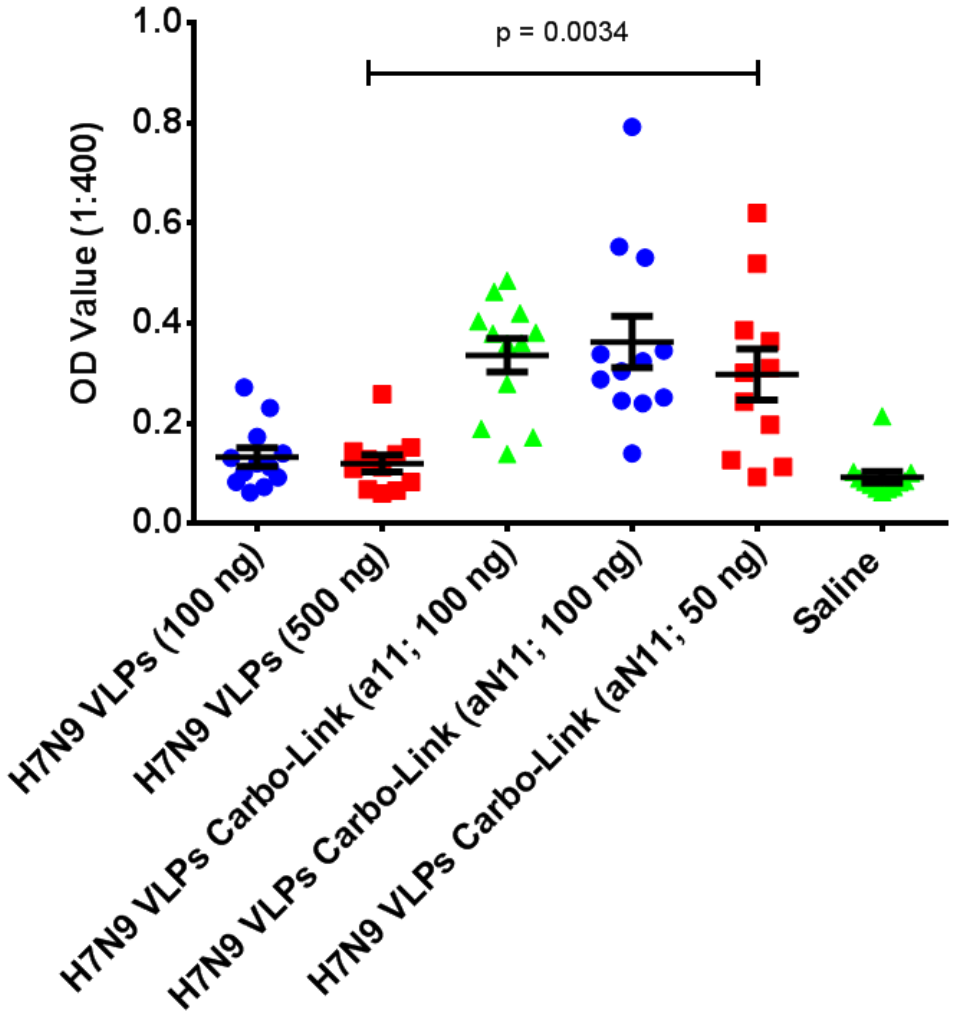
Carbo-Link H7N9 VLP vaccine



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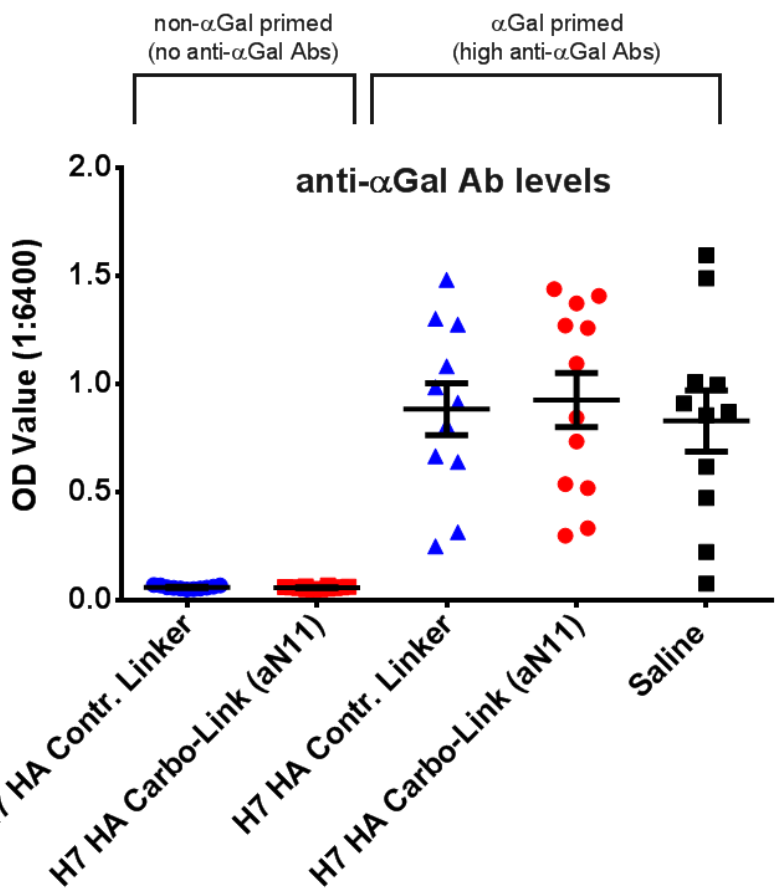
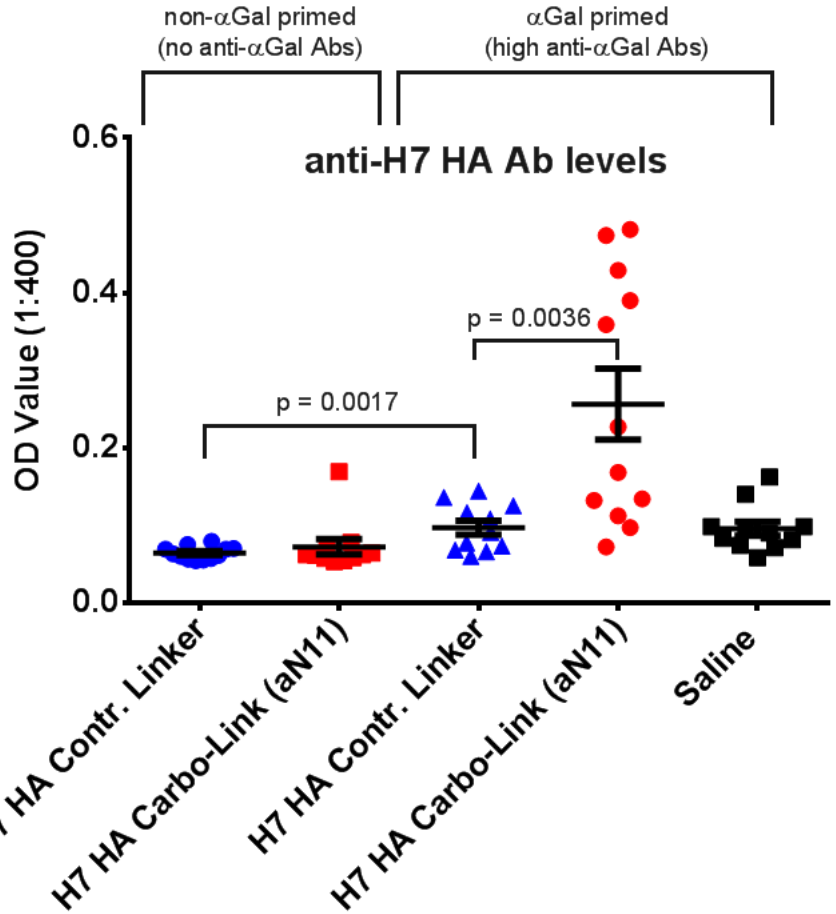
Carbo-Link H7 recombinant protein vaccine





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Conclusions

- We can achieve highly significant vaccine enhancement without any adjuvant
- We can use this linker technology to add αGal to any vaccine of interest (if it was generated in mammalian cells)
- Very high dose sparing capabilities (at least 20x in one instance)
- Does not change the structure of the protein (as evidenced by no change in hemagglutination activity [data not shown])
- Technology is not limited to influenza vaccines