Comparative Potency Study with Monoclonal Antibody Therapy in Development for Prevention of Neonatal Pertussis

Ekaterina Vert-Wong*, Michael Kaleko, Jennifer Maynard, Joseph Sliman

Synthetic Biologics, Inc., Rockville, MD, USA

kvert-wong@syntheticbiologics.com
240-676-2665

Abstract

Objective: Pertussis causes up to 300,000 deaths globally each year. Antibiotic therapy is not efficacious, presumably due to persistence of pertussis toxin. SYN-005, a combination of two monoclonal antibodies, neutralized pertussis toxin, reversed leukocytosis, and accelerated bacterial clearance in mouse and baboon pertussis models. We hypothesize that antibody therapy given at birth has the potential to provide four months of protection and save thousands of lives annually. This study is designed to provide potency and PK data to support this application.

Design and Methods: SYN-005 is composed of two humanized monoclonal antibodies, hu1B7 and hu11E6. The antibodies, alone and in combination, were compared to the WHO international pertussis human antiserum standard by ELISA. SYN-005 elimination kinetics were determined in baboons. We have initiated a baboon prophylaxis study using one monoclonal antibody, 1B7, to generate preclinical proof-of-concept data to test the hypothesis that antibody administration at birth may have a role in the prevention of pertussis.

Results and Conclusion: By ELISA, the potency of 1B7 was 9 ELISA Units (EU)/ug, 11E6 was 1EU/ug, and the combination of 1B7 and 11E6 was 2.1 EU/ug. The half-life in baboons was 11+/- 4 days. By comparison to palivizumab, which has a similar half-life in monkeys and a half-life in humans of 20 days, we calculate that a 40 mg/kg dose of 1B7 in humans will achieve a prophylactic plasma level of 45 EU/ml at four months, well above the 5 EU/ml level, a level considered to be protective for pertussis. Thus, antibody administration at birth has the potential to provide protection during the high risk period for mortality. A study designed to verify five weeks of prophylaxis with 1B7 in newborn baboons, equivalent to that achieved with maternal vaccination, is in progress. Synthetic Biologics intends to pursue clinical development of SYN-005 for both treatment and prevention indications once safety is established.

Background

Pertussis remains a significant public health problem despite near-universal vaccination and continues to cause up to 300,000 deaths worldwide each year, primarily among unvaccinated infants. Antibiotic therapy is ineffective, presumably due to lack of clearance of pertussis toxin, a major virulence factor of the *B. pertussis* bacterium. SYN-005 is a combination of two uniquely potent and synergistic antibodies designed to bind and neutralize pertussis toxin. 11E6 binds to the toxin's S2 and S3 subunits and blocks toxin binding to its target cells. 1B7 binds to both the S1 and S4 subunits, prevents their dissociation within the cell, and blocks the toxic ADP-ribosylase activity of the S1 subunit. SYN-005 is designed to treat pertussis in infants to decrease morbidity and mortality, reduce pediatric intensive care unit (PICU) admissions and shorten hospitalization. Furthermore, SYN-005, or its individual 1B7 component, has the potential to provide prophylaxis for newborns throughout the world that live in circumstances where advanced pediatric critical care services are unavailable. Preliminary justification for this indication is described.

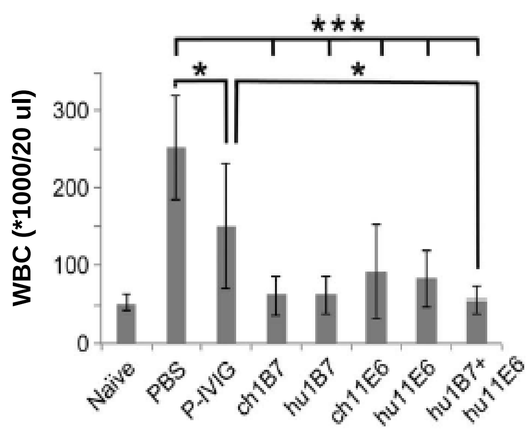
Preclinical Data

Protection of Mice and Therapeutic Effect of Antibody Treatment in Pertussis-Infected Mice and Baboons

Mice were treated with 1B7 and 11E6 antibodies (20 ug total dose) via IP injection 2 hrs prior to infection with $5x10^6$ CFU *B. pertussis* D420 bacteria. Leukocytes, body weight, and bacterial colonization of the lungs were evaluated 10 days later.

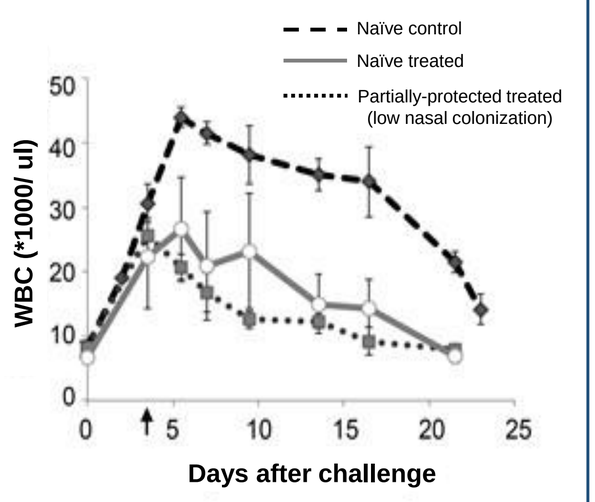
Weanling baboons (n=8) were infected with 10^9-10^{10} CFU of *B. pertussis* D420 bacteria on Day 0 and four were treated on Day 3 with both hu1B7 and hu11E6 (20 mg/kg of each IV).

Mouse Leukocytosis



*P<0.05, **P<0.01, and ***P<0.001 vs PBS treatment

Baboon Leukocytosis



In mice, the humanized antibodies (hu1B7 and hu11E6) protected as well as previous chimeric versions. The individual antibodies and the combination prevented the rise in white blood cell (WBC) count and were more efficacious than P-IVIG, a hyperimmune globulin previously used in human clinical trials. In baboons, treatment with hu1B7 and 11E6 rapidly reversed leukocytosis.

These data demonstrate that SYN-005 was prophylactic in mice and therapeutic in baboons.

Data published in Nguyen et al., Kaleko, and Maynard (2015). "A cocktail of humanized anti-pertussis toxin antibodies limits disease in murine and baboon models of whooping cough". Science Translational Medicine, Dec 2;7(316):316ra195. doi: 10.1126/scitranslmed.aad0966.

Antibody 1B7 Is Undergoing Testing in a Baboon Prophylaxis Model

Currently, maternal vaccination is being evaluated as a possible solution to protect vulnerable newborns from pertussis mortality. As a complementary approach, passive immunization at birth with SYN-005, or its 1B7 component, is anticipated to protect infants during the first four months of life when the risk of fatality from pertussis is greatest. The rationale for 1B7 alone is based, for the most part, on cost constraints in the target regions. Since up to 300,000 newborns die annually in the developing world, this prophylactic strategy has the potential to have a dramatic impact on global health.

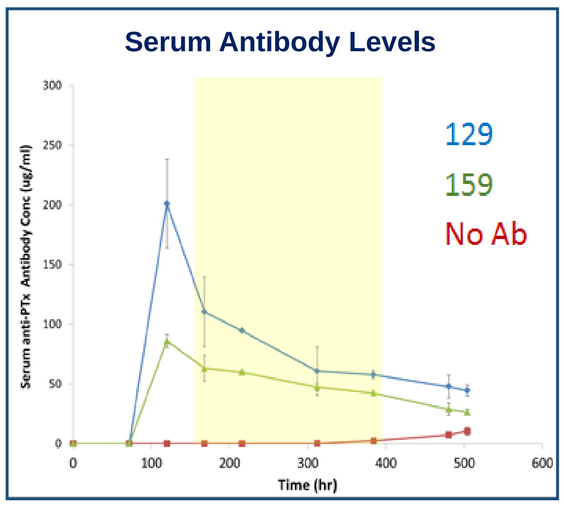
In October 2015, the Gates Foundation awarded a grant to the University of Texas at Austin to generate preclinical proof-of-concept data to test the hypothesis that antibody administration at birth may also have a role in the prevention of pertussis. This study to evaluate the potential of Synthetic Biologics' monoclonal antibody, 1B7, to prevent pertussis in the baboon model has initiated.

Preclinical Data

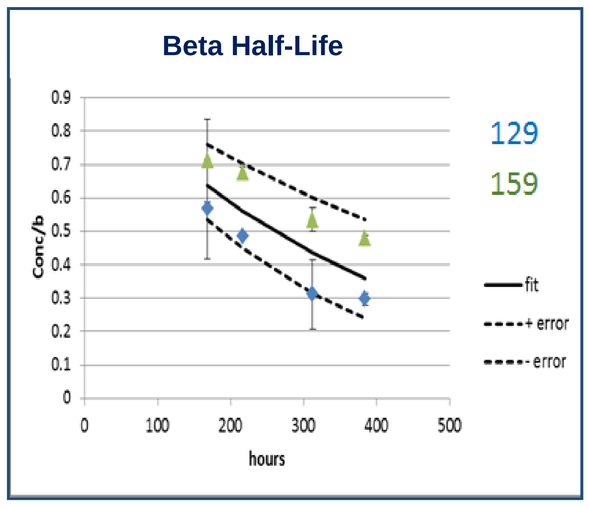
Half-Life Analyses of the Humanized Antibodies in Baboons

To assess the half-life of the SYN-005 humanized antibody cocktail in baboons, the anti-pertussis toxin antibodies were monitored for three weeks. Data from two representative animals is shown below.

Serum Antibody Levels



Beta Half-Life

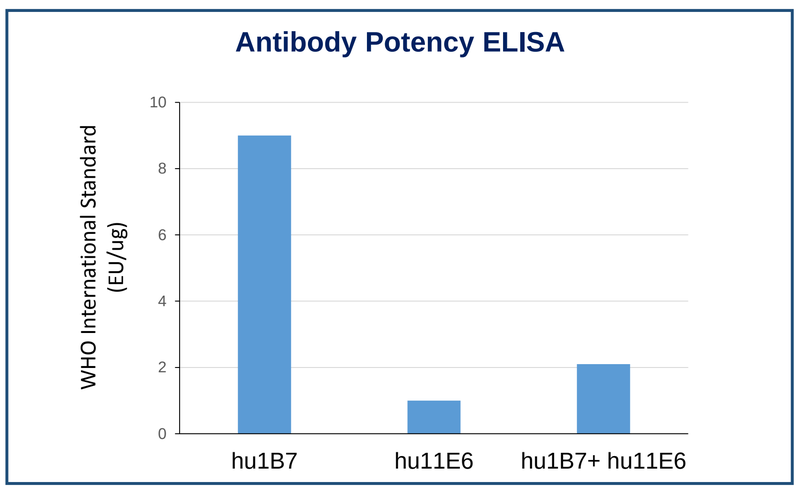


A two-phase elimination profile was observed with a beta phase half-life of 11+/-4 days. The predicted longer half-life in humans suggests that an injection of monoclonal antibody at birth could potentially protect newborns for several months, the high risk period for fatal pertussis.

Comparison of Antibody Potency to the WHO International Standard

The potency of hu1B7, hu11E6, and the combination of hu1B7 and hu11E6, were compared by ELISA to the WHO pertussis human antiserum international standard (WHO International Standard). The ELISA was performed using WHO International Standard for the standard curve.

Antibody Potency ELISA



The hu1B7 antibody showed the greatest potency at 9 EU/ug. The hu11E6 had a potency of 1 EU/ug while the combination of both antibodies had a potency of 2.1 EU/ug.

Ab Therapy May Provide 4 Month Protection

- The potency of antiserum against pertussis toxin is measured via ELISA using the WHO International Standard
- Serum levels of 5 EU/ml are considered protective for pertussis
- 1B7 has a potency of 9 EU/ug
- The half-life in baboons is 11 days
- Based on comparison to palivizumab (which has a similar half-life in monkeys), the human 1B7 half-life is anticipated to be at least 20 days
- An IM dose of 40 mg/kg is expected to yield serum levels at 1 month of >100 ug/ml and at 4 months of ≈5 ug/ml
- 5 ug/ml equates to 45 EU/ml, well above the threshold for protection
- 1B7 provides an additional margin for protection since it was identified based on its potency for toxin neutralization whereas only a fraction of the antibodies in the WHO polyclonal preparation are neutralizing

Conclusions

- Animal studies support SYN-005 clinical application
  - For the treatment of critically ill infants to reduce morbidity, mortality, long-term complications, and hospital intensive care unit stays
  - To provide protection to high risk newborns through their first 4 months, the period associated with the highest mortality
- The monoclonal antibodies have the potential to be used individually or in combination
- Research efforts are currently directed towards a proof-of-concept baboon study with 1B7 to support the prophylactic indication

SYN-005 has the potential to become the first agent designed to treat and prevent pertussis by neutralizing pertussis toxin

The SYN-005 program is being performed in collaboration with Intrexon Corporation and is based on science, technology, intellectual property and data developed in collaboration with the University of Texas at Austin's Cockrell School of Engineering, in the laboratory of Assistant Professor, Jennifer Maynard, Ph.D.